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SYMPOSIUM ON CHOLINE SALICYLATE

GUEST EDITOR—ROBERT H. BROH-KAHN, M.D.

Choline Salicylate: A New, Effective, and Well-Tolerated Analgesic, Anti-inflammatory, and Antipyretic Agent — ROBERT H. BROH-KAHN

Choline Salicylate: A New and More Rapidly Absorbed Drug for Salicylate Therapy — JULIUS WOLF AND REUBEN ABOODY

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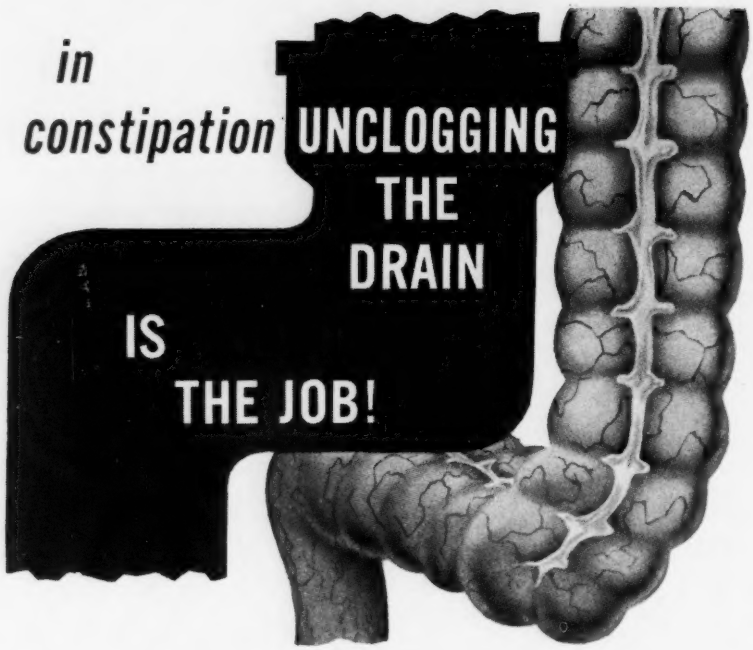

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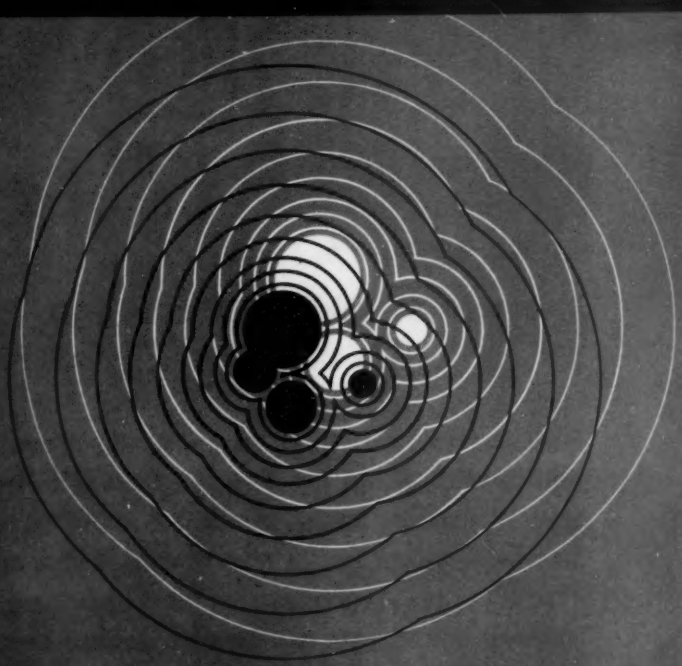

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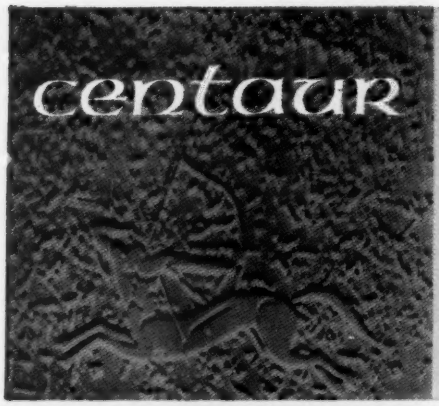

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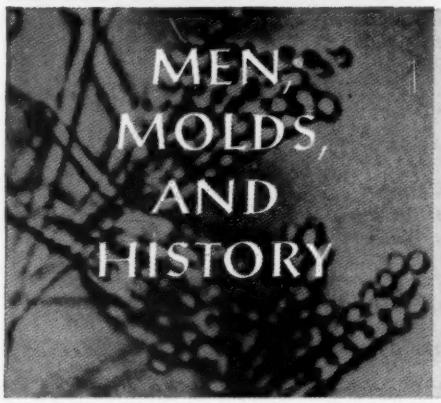

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Symposium on Choline Salicylate
GUEST EDITOR—ROBERT H. BROH-KAHN, M.D.

Choline Salicylate: A New, Effective, and Well-Tolerated Analgesic, Anti-inflammatory, and Antipyretic Agent

Robert H. Broh-Kahn, M.D.
CONSULTANT, BUREAU OF ADULT HYGIENE, NEW YORK CITY DEPARTMENT OF HEALTH
NEW YORK, N. Y.

By virtue of their relatively nontoxic nature and their pronounced analgesic, anti-inflammatory, and antipyretic properties, salicylates are more widely prescribed and used than any other single class of drug. Although a host of salicylates and salicylate derivatives have been prepared, described, and evaluated, pharmacologically and clinically, only sodium salicylate and acetylsalicylic acid have met with real acceptance by the medical profession. This appears somewhat surprising since the undoubted value of these time-honored remedies is to good measure offset by some of their disadvantages. Acetylsalicylic acid, for example, not only is known to induce considerable gastric distress in an appreciable segment of the population, particularly when administered in the high dosages required for its full therapeutic effect, but more recently has been incriminated as a cause of an erosive gastritis.[1] Acetylsalicylic acid is notoriously poorly tolerated by patients with peptic ulcer and gastritis. Further, the loss of blood from the gastrointestinal tract—either in the form of occult blood in the stool[2,3] or in the form of frank gastrointestinal hemorrhage[4,5]—represents an even more insidious complication of its use. The drug also has the disadvantages of extreme insolubility and instability in water, which preclude its use in liquid formulations.

In more recent years, attempts have been made to minimize some of these disadvantages of acetylsalicylic acid by administering it in mixtures with alkalies or so-called buffering agents. These latter have been alleged both to decrease the

incidence of gastric irritation and to promote the rate of absorption of the drug into the blood,[6,7] although it would appear that the evidence of these effects is somewhat equivocal at best, since controlled studies[8,9] have failed to confirm either of such claims. Unequivocal evidence, however, exists that the simultaneous administration of alkali with salicylates accelerates the rate of excretion of the latter through the kidney.[10] Thus, even if such agents did increase the rate of salicylate absorption, such an effect would be rendered pharmacologically meaningless as a result of increased rate of elimination of the drug from the body.

Sodium salicylate, on the other hand, has been described as even more irritating to the gastrointestinal tract.[11] It is commonly administered in the form of enteric-coated tablets, a practice that not only impedes the rate of absorption of the drug but that even renders any absorption haphazard at the best.[12] High dosages of sodium salicylate are, of course, believed to be contraindicated in patients with certain types of cardiovascular, renal, and hepatic disease and other conditions in which it is considered advisable to restrict the intake of sodium ion.

In view of such considerations, the availability of a salicylate possessing the therapeutic properties of this type of drug but lacking some of the disadvantages would appear highly desirable. Since past experience had indicated that choline salts of some organic acids possessed certain desirable properties,[13,14] it therefore appeared of interest to synthesize, characterize adequately, and evaluate the therapeutic properties of choline salicylate,* the choline salt of salicylic acid.

HISTORICAL BACKGROUND

It appears somewhat surprising that although choline salts and salicylates have both been intensively studied, a search of the literature has failed to reveal reference to choline salicylate as such, or to its properties or its medical use, prior to the initiation of this present study. The synthesis of the salicyl ester of choline, salicyl-choline (analogous to acetylcholine), has been described.[15] An alleged reaction product between choline and salicylic acid was also referred to in passing by Johnson,[16] who reported a reaction system between an alcoholic solution of choline base and some organic acids such as the iodobenzoic acids and *p*-amino-phenyl-arsonic acid, among which salicylic acid was noted as an example. Representative descriptions of the reactions with some of the acids were reported, but not in the case of salicylic acid. At any rate, the reaction products were neither isolated, purified, identified, nor characterized since the author noted merely that attempts at isolation by concentration of the reaction media by vacuum distillation yielded only viscid, sirupy masses. As a result of this failure to isolate or identify the alleged products, the author confessed that he was unable to state whether they represented choline salts of the acids or some other type of product. It appears highly improbable that Johnson actually prepared choline salicylate since it was found impossible to isolate it by duplicating his description of this reaction.[17]

On the other hand, we[18,19] have succeeded in synthesizing, isolating, identifying,

*The trade name of The Purdue Frederick Co. for choline salicylate is Arthropan. The drug was supplied by the Medical Department for this study.

and characterizing choline salicylate and desire to report some of its properties and some observations concerning its pharmacological and therapeutic activities.

SYNTHESIS AND PROPERTIES OF CHOLINE SALICYLATE

Although choline salicylate may be prepared by a number of procedures,[18] it is readily obtained in the pure state by reacting equimolecular quantities of a metallic salicylate, such as sodium salicylate, with an inorganic salt of choline, such as choline chloride, in an acetone or other aqueous-miscible solvent medium. In this procedure, the sodium chloride formed from the reaction is precipitated and removed by filtration. The addition of a nonaqueous solvent, miscible with acetone, such as petroleum ether, precipitates the choline salicylate from the filtrate. The precipitate, dissolved in the minimum amount of warm acetone, can be recrystallized by cautious addition of the appropriate quantity of a lipid solvent such as petroleum ether and then cooling.

Freshly prepared and thoroughly dried choline salicylate is a white (colorless) crystalline solid melting at 49.5 to 50.0 C. As such, its elementary analysis conforms to that of the anhydrous choline salt of salicylic acid. As shown in figure 1, it has a molecular weight of 241 of which 57 per cent is represented by its salicylate content. Choline salicylate is extremely soluble in water, alcohol, acetone, and similar solvents and insoluble in ether, petroleum ether, benzene, and other lipid solvents. It is easily the most water soluble of all salicylates, a saturated aqueous solution containing 96 per cent choline salicylate by weight. Choline salicylate is excessively hygroscopic, and as a result of this property plus its extreme solubility, it is converted almost immediately on exposure to air, first into a pasty mass and then into a sirup. As a consequence it is not practically feasible to maintain choline salicylate in the solid state and it has not been found possible to date to handle it as such except as a transitory laboratory curiosity. For such reasons, the observations described herein have been obtained through use of an aqueous solution of this material.

Aqueous solutions of choline salicylate prepared under the most stringent conditions of purity are colorless, odorless, and possess the characteristic bitter taste and aftertaste of other salicylates. In ordinary practice, solutions of this compound display a light amber shade presumably due to traces of iron in the reaction system, which form colored complexes with the salicylate. The compound exists, in aqueous solution, in the form of its dissociated choline and salicylate ions. A 10 per cent solution has a *p*H of approximately 6.5 and appears to be stable for almost indefinite periods of time when stored under ordinary conditions. The addition of strong acid

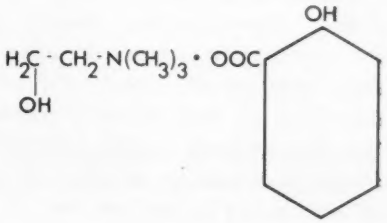

FIG. 1. Structural formula of choline salicylate.

TABLE I

*Relative Plasma Total Salicylate Levels (mg./liter) After the Oral Administration of Equivalent Quantities of Acetylsalicylic Acid and Choline Salicylate, Both Providing 500 mg. Salicylate**

	Time after administration									
	10 minutes		20 minutes		60 minutes		120 minutes		360 minutes	
Subject	Aspirin	Choline salicylate	Aspirin	Choline salicylate	Aspirin	Choline salicylate	Aspirin	Choline salicylate	Aspirin	Choline salicylate
A	4.2	26.7	6.7	23.7	19.7	26.3	28.6	14.2	18.3	13.4
B	2.8	25.5	8.6	20.9	22.8	24.3	25.3	18.1	14.7	10.3
C	1.9	3.9	10.5	10.3	17.8	33.0	24.4	27.4	14.2	12.3
D	7.8	26.7	13.7	32.8	22.0	30.5	27.6	22.8	12.3	16.9
E	4.7	61.1	18.1	73.7	27.9	44.1	36.8	41.6	24.0	40.8
F	21.8	45.9	41.6	52.8	42.4	36.9	10.1	36.1	13.4	21.1
G	16.1	45.0	32.5	41.4	50.0	38.6	51.4	27.9	25.8	18.7
H	10.6	38.9	11.4	55.6	26.5	38.1	32.1	30.6	7.0	15.0
I	12.5	35.8	28.1	35.8	38.6	30.2	42.3	29.6	25.5	14.2
K	2.0	52.3	5.0	47.3	17.9	34.7	15.9	35.6	10.9	18.6
L	2.2	50.0	7.3	50.3	26.5	36.1	23.2	27.2	11.4	11.4
M	8.4	27.6	11.9	27.9	36.4	32.4	68.1	15.6	13.3	10.9
Mean	7.9	36.6	16.3	39.4	29.0	33.8	32.2	27.2	15.9	17.0
Standard error	1.83	4.49	3.31	5.10	3.02	1.58	4.57	2.43	1.78	2.38

* These salicylate determinations were kindly performed by Dr. Paul K. Smith, professor and head of the Department of Pharmacology, George Washington University School of Medicine, Washington, D. C.

in the cold immediately precipitates free salicylic acid, whereas choline base, readily recognized by its characteristic fecal odor, is instantly liberated on the addition of strong alkali. These and other reactions confirm the fact that the compound in question is the choline salt of salicylic acid.

PHARMACOLOGY

All observations to date indicate that when the drug is administered in conventional dosages, the effects of choline salicylate are typical of and resemble those of other salicylates. Consequently, a detailed description of these effects is considered unnecessary.

Toxicity in Animals. Toxicity of the drug in laboratory animals has been determined. The acute oral toxicity in rats, as estimated by conventional procedures and expressed in terms of the LD_{50}, is 1.53 ± 0.15 Gm./Kg. of body weight, a figure that approximates closely the LD_{50} reported for acetylsalicylic acid.[20] Choline salicylate has been administered daily to rats and dogs in dosages as high as 0.5 Gm./Kg. of body weight for a period of six months without eliciting any clinical evidences of toxicity or other signs of intolerance. (By contrast, a dosage of 40 gr. of acetylsalicylic acid per day to a patient weighing 70 Kg. may be expressed as

0.038 Gm./Kg. of body weight.) Choline salicylate may therefore be considered nontoxic according to conventional usage of the term.

Percutaneous Absorption. When solutions or lotions or ointments containing choline salicylate are applied to the shaved but unbroken skin of rabbits, detectable amounts of salicylate rapidly appear in the blood and significant quantities are found in the urine. Accordingly, choline salicylate is rapidly absorbed by the percutaneous route. Qualitatively similar observations indicate that the same is true in man.

Rate of Absorption in Man. When choline salicylate is given by mouth to man, it is absorbed very rapidly into the blood. In order to determine the absolute rate of its absorption and to compare it with the rate for acetylsalicylic acid, both drugs were administered in equivalent quantities to each of a series of 12 normal fasting adults. The choline salicylate was administered as 1 teaspoonful (5 ml.) of a cherry-flavored solution containing 870 mg. choline salicylate and the acetylsalicylic acid as two 5-gr. (650 mg.) aspirin tablets. Half of the subjects received the choline salicylate followed by 125 ml. water and the other half the two aspirin tablets with the same amount of water. After a rest of four days to ensure elimination of all salicylates from the body, the same procedure was repeated but acetylsalicylic acid was given to those who had previously received choline salicylate, whereas those who had previously received the acetylsalicylic acid were given the choline salicylate. Each subject thus, in turn, received 500 mg. salicylate in the form of one or other of the two drugs and so served as his own "control." Blood was drawn by venipuncture at 10, 20, 60, 120, and 320 minutes after ingestion of either drug and the plasma total salicylate determined in each by a modification of the method of Brodie, Udenfriend, and Coburn.[21] The results are summarized in table I and illustrated graphically in figure 2.

It is readily apparent that choline salicylate is absorbed at a very rapid rate and approximately five times more rapidly than aspirin. Thus, at the end of 10 minutes,

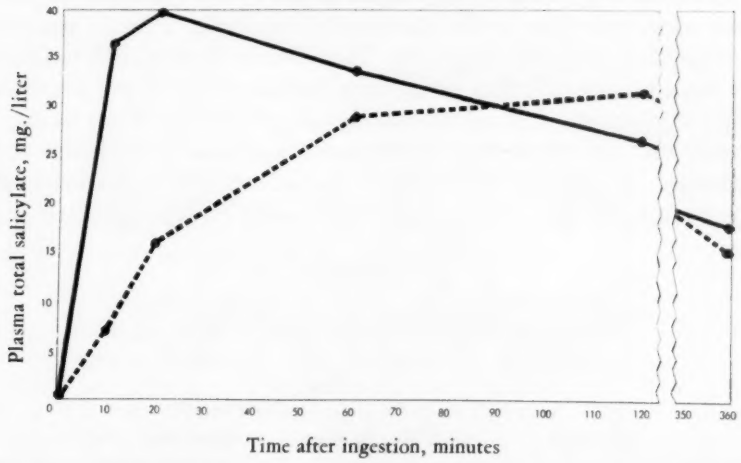

FIG. 2. Total plasma salicylate levels in normal adults after ingestion of equivalent amounts of choline salicylate and aspirin (500 mg. of salicylate in each). Solid line: After 871 mg. of choline salicylate. Broken line: After 650 mg. of aspirin.

TABLE II

Analysis of Variance of Plasma Salicylate Levels in Table I

Source of variation	Degrees of freedom	Sum of squares	Mean square	Computed F
Main effects:				
Among subjects	11	5233.63	475.78	5.38*
Between drugs	1	3332.75	3332.75	37.70*
Among times	4	3617.29	904.32	10.23*
First order interactions:				
Subjects x drugs	11	3538.47	321.68	3.64†
Subjects x times	44	1552.96	35.29	‡
Times x drugs	4	5097.43	1274.36	14.41†
Error	44	3890.17	88.41	
Total	119	26,262.70		

* $P > 0.001$.
† $P > 0.01$.
‡ Not significant.

the plasma total salicylate levels after choline salicylate were approximately five times as high as after acetylsalicylic acid.

Statistical analysis of these data reveal extremely significant differences between these rates of absorption of the two drugs. The results of an analysis of variance, with three sources of variation (the times at which the blood levels were drawn, the differences between the two drugs and between the subjects themselves), are presented in table II and amply confirm the fact that the differences between the two drugs contribute to a highly significant degree ($P < 0.001$) to the differences between the mean salicylate levels illustrated in figure 2. Further analysis, as in table III, emphasizes this and other facts. It is obvious that the differences between the higher mean plasma salicylate levels after choline salicylate and the lower mean levels after acetylsalicylic acid are highly significant and significant at the 10- and 20-minute intervals ($P < 0.01$; $P < 0.05$) but not significantly dissimilar at 60, 120, and 320 minutes. In other words, although choline salicylate is obviously absorbed at a much more rapid rate than acetylsalicylic acid, choline salicylate maintains

TABLE III

Significance of Differences Between Mean Plasma Salicylate Levels (Table I) After Choline Salicylate and Aspirin at Various Times

	Time				
	10 minutes	20 minutes	60 minutes	120 minutes	360 minutes
P	<0.01	<0.05	n. s.	n. s.	n. s.

n. s. = Not significant.

plasma salicylate levels equally as well and for as prolonged a period as the latter drug. Thus, since the plasma salicylate levels are so much higher after choline salicylate during early stages after its ingestion and not dissimilar to those after acetylsalicylic acid during the later period, it is apparent that the mean plasma salicylate level after choline salicylate is significantly higher than that after aspirin for a minimum period of at least six hours after ingestion of equivalent quantities of either drug.

Other equally interesting facts are revealed by further statistical analysis of the data in table I. Table IV demonstrates the lack of significant differences between the plasma salicylate levels at 10 and those at 20, 60, and 120 minutes. In other words, since these levels do not differ significantly from one another, peak plasma salicylate levels are attained as early as 10 minutes after ingestion of choline salicylate as contrasted to the 120 or more minutes required to attain such peak levels after ingestion of aspirin.[22] In contrast, the levels at 120 minutes after aspirin ingestion are significantly higher than those at 10 minutes. Thus, not only is choline salicylate absorbed five times more rapidly than acetylsalicylic acid, but it also elicits peak plasma salicylate levels at least 12 times more rapidly than aspirin.

Such demonstrations of the incomparably more rapid rate of absorption of choline salicylate than of aspirin have subsequently been repeatedly confirmed.[23–26] Comparison of these and other data indicate that choline salicylate is much more rapidly absorbed not only than acetylsalicylic acid but also more so than other salicylates also alleged to be more rapidly absorbed than aspirin, namely, the so-called "buffered aspirin" and the so-called "soluble aspirin" or calcium acetylsalicylic acid carbamide. It is also noteworthy that the magnitude of the differences between the rates of absorption of choline salicylate and acetylsalicylic acid is so great that the statistical

TABLE IV

Significance of Differences Between Plasma Salicylate Levels (Table I) After Choline Salicylate and Aspirin at Various Times

Times	Probability values (P)	
	Choline salicylate	Aspirin
10 vs. 20 minutes	n. s.	n. s.
10 vs. 60 minutes	n. s.	<0.01
10 vs. 120 minutes	n. s.	<0.01
10 vs. 360 minutes	<0.01	n. s.
20 vs. 60 minutes	n. s.	<0.05
20 vs. 120 minutes	<0.05	<0.05
20 vs. 360 minutes	<0.01	n. s.
60 vs. 120 minutes	n. s.	n. s.
60 vs. 360 minutes	<0.01	<0.05
120 vs. 360 minutes	<0.05	<0.01

n. s. = Not significant.

significance of this difference can readily be demonstrated in small samples of 12 or less, whereas it has been necessary to utilize large samples to demonstrate alleged differences of a much smaller magnitude between the rates of absorption of aspirin and buffered or soluble aspirin.

CLINICAL EVALUATION OF CHOLINE SALICYLATE

Clinical experience has demonstrated that it is possible to obtain an adequate and competent evaluation of the properties and effects of a new drug only after it has been used for prolonged periods of time, in a wide variety of conditions and patients, and by a large number of physicians. Any other procedure almost inevitably removes the element of randomness from the sample comprising the study and incurs the danger of introducing too many uncontrolled variables including, of course, such poorly defined ones as the subjective reactions of the patients, the degree of their satisfaction with results of their previous treatment, and, above all, the attitude of the investigator himself in his emotional approach to the use of a new drug. Consequently, rather than restricting ourselves to a study of the use of choline salicylate in the relatively circumscribed clinical facilities available to us for this purpose, we enlisted the cooperation of numerous physicians throughout the United States and Canada.

Prior to their use of the drug, these physicians had been informed of the rapidity of its rate of absorption, the demonstration of its lack of toxicity in animals, and the preliminary clinical observations that it appeared to produce effects qualitatively similar to those of other salicylates and that it was apparently sufficiently well tolerated in man to justify its cautious and careful use in dosages equivalent to those commonly prescribed for acetylsalicylic acid. These physicians were then requested to evaluate the effects of choline salicylate in their own clinics and practices and, in order to obtain a ready frame of reference, to compare its effects with those of the standard of all salicylates—acetylsalicylic acid. This latter comparison was accomplished by one or more of the following procedures:

In the case of patients previously treated with aspirin and whose response to aspirin had been accurately defined, the previous medication was withdrawn, treatment with choline salicylate was initiated, and the responses to the two drugs were compared.

In many instances where previous response to aspirin had not been accurately defined by the investigator himself, the responses to the two drugs were evaluated by a crossover study in which the drugs were administered and their effects observed during different periods of treatment. However, of necessity, the physical dissimilarity between the two drugs precluded use of a blind or double-blind technique.

In a relatively small number of instances where a previous response to acetylsalicylic acid had not been personally evaluated by the investigator and where the exigencies of practice were considered to preclude a crossover type of study, the comparative evaluation was based solely on the carefully observed reactions to choline salicylate as contrasted with the investigator's previous experience with aspirin in his patient population at large.

It is noteworthy that a detailed analysis of the results reported in this evaluation failed to disclose any essentially dissimilar findings irrespective of the type of procedure on which the comparative evaluation was based.

In these studies, choline salicylate was administered in the form of a cherry-flavored solution, each teaspoonful (5 ml.) containing 870 mg. active drug, a quantity providing 500 mg. salicylate and thus equivalent to 650 mg. (10 gr.) of acetylsalicylic acid. The latter was usually administered as the usual 5 gr. commercial aspirin tablet, but in some instances it was given in the form of a brand of buffered aspirin or combined with such additives as acetophenetidin and caffeine, para-aminobenzoic acid, ascorbic acid, etc.

This report summarizes the results obtained by some 80 investigators* who administered and observed the effects of choline salicylate in approximately 1200 patients, treated daily for periods up to one year. The patients were divided rather equally as to sex and ranged in age from infants of a few months up to 80 years or more. The majority were adults and were treated for a variety of conditions of which rheumatoid arthritis, osteoarthritis, and rheumatic fever were the most common. Various other musculoskeletal disorders, gout, headache, dysmenorrhea, post-immunization pyrexia, and other miscellaneous disorders were also treated.

RESULTS

All investigators reported that the therapeutic and other effects of choline salicylate qualitatively resembled those of other salicylates. Choline salicylate was described as an effective analgesic, anti-inflammatory, and antipyretic agent. As with other salicylates, overdosage elicited symptoms of salicylism and, in some instances, gastrointestinal complaints.

The results of the comparative evaluation with acetylsalicylic acid were of great interest. If one assumes a random distribution of competency among the investigators and that the sample of patients was truly representative and randomly distributed in regard to such factors as severity of disease, degree of response to medication, etc., it could be predicted that, if the two drugs under study possessed identical properties or if the two drugs had in fact been identical but presented with different appearances (shape, size, color, physical form, etc.), the report of the results of their use should have been characterized in the pattern of a normal frequency distribution as illustrated in figure 3. In other words, even if the two drugs had exactly the same activities, a small number of investigators, as a result of their observations on a small number of patients, should have reported one drug as essentially "inferior" to the other and an equally small number of investigators, working with a similar small sample of patients, should have reported the first drug as "superior" to the second. On the other hand, the largest number of investigators, reporting on results with the majority of patients, should have concluded that the effects of the two drugs were essentially similar.

The results reported in regard to four different categories of reaction of the patients

*For the sake of brevity the names and addresses of these investigators are not listed in this article but will be furnished, on request, by the author.

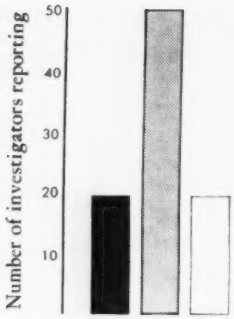

FIG. 3. Anticipated distribution of reported results if choline salicylate and acetylsalicylic acid possessed similar activities. Black column: Choline salicylate "better than" aspirin. Gray column: choline salicylate "same as" aspirin. White column: Choline salicylate "poorer than" aspirin.

to the drugs were actually distributed according to the frequency pattern illustrated in figure 4. It is clearly evident that these results were markedly skewed away from the normal distribution frequency "in favor of" choline salicylate.

We consider it entirely valid to conclude from these data that, in the sample of patients reported on and in respect to the reactions cited, choline salicylate displayed a more favorable effect than aspirin. Further, in view of the size of the patient sample and the number and geographical distribution of the investigators, we are inclined to conclude that the same generalization can be extended to the population at large.

This, of course, does not imply that choline salicylate, even in respect to the considered actions, will prove superior to acetylsalicylic acid in every patient. Indeed, as is clearly illustrated in figure 4, an appreciable number of patients responded more favorably to aspirin. It does indicate that, if consideration is confined to the issues here discussed, a greater number of patients will respond more favorably to choline salicylate than to aspirin, that one can predict the greater probability of a more favorable response to choline salicylate, and that, whereas aspirin may prove the drug of choice over choline salicylate in some patients, choline salicylate should, on

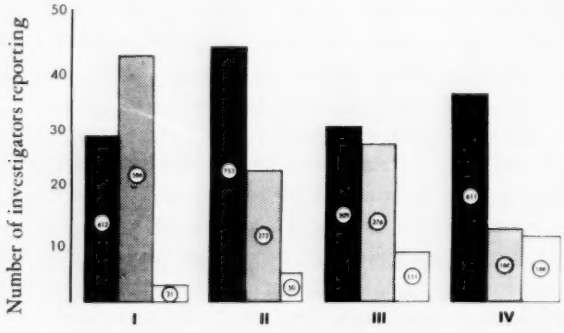

FIG. 4. Distribution of results reported in comparative evaluation of properties of choline salicylate and acetylsalicylic acid. Figures in circles indicate number of patients comprising samples on which evaluation was based. Black columns: Choline salicylate "better than" aspirin: (I) more rapid onset of action, (II) greater freedom from gastrointestinal side reactions, (III) greater dosage tolerated, (IV) more easily administered. Gray columns: Choline salicylate "same as" aspirin. White columns: Choline salicylate "poorer than" aspirin.

purely statistical grounds, be considered the drug of choice over aspirin in initiating salicylate therapy in all patients.

These data merit some more detailed comments. "Rapidity of onset of action" refers, of course, to rapidity of effect after instituting therapy. If a therapeutic effect is at all dependent on the attainment of a given minimum plasma salicylate level, since the latter is attained so much more rapidly after choline salicylate, it could be anticipated that the onset of action of choline salicylate would be reported to be more rapid than that of acetylsalicylic acid, as is apparently illustrated in figure 4. We are inclined to regard this conclusion with some reservation. In the first place, it is impossible to estimate the influence exerted on the investigator in forming this opinion by his knowledge beforehand of the more rapid rate of absorption of choline salicylate. In the second place, since no reliable procedures are available to quantitate small differences in intensity of pain or anti-inflammatory effect in man, it is obviously impossible to determine accurately the rapidity of such effects. Antipyretic effects can, of course, be accurately estimated but it is almost impossible to design or achieve in man a rigidly controlled study of this sort. It has been possible to demonstrate a significant antipyretic effect of choline salicylate as early as 10 minutes after its administration,[27] but, as noted previously, comparison of this effect with that obtained after aspirin is impractical. Thus, whereas a sound pharmacological basis undoubtedly exists for a more rapid onset of action of choline salicylate, logical considerations imply that its more rapid therapeutic effect cannot presently be regarded as having been conclusively demonstrated.

The importance of rapidity of onset is most dramatically emphasized in treatment of acute episodes such as headache. However, even in treatment of chronic conditions such as rheumatoid arthritis, the speed of onset of action assumes importance because of the rapidity with which the first dose of choline salicylate after awakening has been reported to provide relief from the characteristic early morning joint stiffness of this disease.

The results shown in figure 4 indicate that choline salicylate elicited a lower incidence of gastrointestinal distress—pyrosis, nausea, retching, vomiting, etc.—than acetylsalicylic acid. These results refer to the incidence of such side effects after equivalent dosages of the two drugs. Thus, choline salicylate in dosages providing 2 Gm. of salicylate per day elicited fewer instances of gastrointestinal distress than equivalent dosages of acetylsalicylic acid, and the latter in dosages providing 4 Gm. of salicylate per day induced more side effects than equivalent quantities of choline salicylate, etc.

The accurate estimation of incidence of gastrointestinal irritation was complicated by a different complaint induced in some patients by choline salicylate. The cherry-flavored formulation was considered too sweet by some adults who complained that it tended to become distasteful to them after several weeks. This is an entirely different type of reaction than that caused by aspirin, and it was later found that the reaction could be minimized or dissipated altogether by diluting the dosage in water or some beverage before swallowing. Some persons also complained of an aftertaste and this also was found to become negligible if water was swallowed immediately after the drug or if chewing gum or a flavored lozenge was taken. The complaints

of unpalatability, etc., were included with those of true gastrointestinal distress since it was not considered valid, during this comparison, to exclude them from the tally. However, the incidence of the true type of gastrointestinal irritation induced by aspirin and other salicylates is undoubtedly much lower after choline salicylate.

One aspect of the undoubtedly greater gastric tolerance to choline salicylate was noted at an early date. Most patients with peptic ulcer and various types of gastritis tolerate acetylsalicylic acid very poorly since even small dosages induce severe epigastric distress. It rapidly became evident that many such patients, who were unable to tolerate aspirin, could take average and even high dosages of choline salicylate without gastric irritation.

Admittedly, gastrointestinal complaints are subjective in nature, but recently there has been adduced entirely objective evidence that both acetylsalicylic acid and the so-called soluble aspirin, calcium acetylsalicylate carbamide, are definitely more irritating to the gastrointestinal tract than choline salicylate. Both of the former have been demonstrated to induce a greater quantity of loss of blood in the stool, whereas administration of choline salicylate induces no blood loss.[28] This was demonstrated by the ingenious procedure of tagging the subject's red cells with Cr^{51} and determining the amount of radioactivity appearing in the stool after the subjects received equivalent amounts of the three drugs. Such concrete evidence that, of all salicylates yet tested, choline salicylate was the least irritating to the gastrointestinal tract provides a firm explanation for the lower incidence of gastrointestinal distress after choline salicylate than after aspirin.

The results shown in figure 4 also indicate that many patients tolerated a higher maximum dosage of choline salicylate than of acetylsalicylic acid. That is to say that higher dosages of choline salicylate could be administered before the appearance of side effects. Thus, whereas a patient may have been able to tolerate only 40 gr. of acetylsalicylic acid per day without gastric distress, the same patient tolerated choline salicylate in excess of the equivalent of 80 gr./day. This phenomenon again is undoubtedly another reflection of the fact that choline salicylate is less irritating to the gastrointestinal tract.

Individual patients have varied widely in their tolerance to choline salicylate. The maximum daily dosage reported to date to have been tolerated without side effects has been 20.9 Gm., equivalent to 240 gr. of acetylsalicylic acid. Tolerance to such high dosages should be considered atypical, but careful clinical studies have revealed that a great many patients tolerated well, for prolonged periods of time, daily dosages of from 7 to 10.4 Gm., equivalent to 80 to 120 gr. of aspirin. By contrast, most of the investigators reported that their average ambulatory patient with arthritis could not tolerate, day after day, daily dosages of acetylsalicylic acid in excess of 40 to 60 gr. without the appearance of gastrointestinal distress.

Whereas the supervention of gastric distress has usually been the factor limiting the maximum tolerated dosage of acetylsalicylic acid, the maximum tolerated dosage of choline salicylate by contrast has most frequently been defined by that level at which salicylism occurs. In other words, as the dosage of aspirin was increased, the appearance of gastric distress precluded any further increase. Thus, in at least 30 per cent of the patients with rheumatoid arthritis, it was found impossible to administer

a dosage sufficiently high to elicit the symptoms of salicylism because of the severe gastric distress appearing at a considerably lower dosage. On the other hand, as the dosage of choline salicylate was increased, the limits of tolerance were frequently attained only after appearance of salicylism and without any previous indication of gastric distress. As a consequence, it was possible to administer a sufficiently high dosage to increase the plasma salicylate levels to those values at which salicylism ensues.

These facts are of great significance in the treatment of rheumatoid arthritis, in particular. Most rheumatologists concur that the maximum therapeutic effect obtainable from salicylates is by use of the highest dosage that can be tolerated just below that at which salicylism appears. However, as noted previously, the severe gastric distress induced by much lower dosages of acetylsalicylic acid and other salicylates precludes their administration in such high dosages and it is therefore impossible to utilize them to the maximum benefit. Choline salicylate overcomes this impasse in many patients since it can be given to so many in such high dosages as to induce the toxic manifestations of salicylism without the earlier appearance of gastric distress. Thus, many patients with rheumatoid arthritis have been able to realize for the first time, through use of choline salicylate, the theoretical maximum therapeutic potential of salicylate therapy.

The results shown in figure 4 indicate that the investigators and their patients considered choline salicylate easier to administer than acetylsalicylic acid. Such a conclusion is the result of the fact that choline salicylate is the first salicylate available which, as a stable liquid medication, may safely and readily be administered in high dosages to every type of patient. It was described as much easier to administer than tablets of acetylsalicylic acid not only to infants and children but to many adults who, due to pharyngeal, esophageal, or neurological disease, idiosyncrasy, or inconvenience, had difficulty in swallowing tablets or capsules, especially when prescribed in numbers. For example, a daily dosage of 120 gr. of acetylsalicylic acid requires the patient to swallow 6 tablets at a single dose; the equivalent of choline salicylate is administered as 1 tablespoonful.

The evaluation of the comparative therapeutic effectiveness of choline salicylate and acetylsalicylic acid was not included in figure 3. Many investigators reported choline salicylate to be the more effective of the two drugs. We are disinclined to accept such a conclusion without further studies, since so many factors other than the intensity of the therapeutic effect itself influence the apparent degree of the latter. Obviously, if, in acute episodes, relief is afforded more rapidly by choline salicylate than by aspirin, both patient and physician may be misled into considering choline salicylate the more effective of the two. If patients, for one reason or another, cannot tolerate fully effective dosages of aspirin but can tolerate such dosages of choline salicylate, again a misleading impression may be gathered that the latter drug is the more effective. We believe, however, that the degree of effectiveness of a salicylate is a function up to a certain maximum of the plasma salicylate level resulting from its administration. All things being equal, one would anticipate equal therapeutic effects from two salicylates provided that similar plasma salicylate levels resulted from the administration of each. Rather than stating that choline salicylate is a

more effective or potent drug than acetylsalicylic acid, we conclude that the data indicate that more patients obtained greater benefit from choline salicylate than from acetylsalicylic acid. This may appear to be an exercise in semantics, but it avoids an otherwise untenable pharmacological conclusion. There was certainly no evidence that choline salicylate was less effective than other salicylates.

DISCUSSION

We have reported here results obtained in a cooperative, large-scale evaluation of the properties of choline salicylate and a comparison of these with those of acetylsalicylic acid. We have indicated the reasons why it is believed that such an evaluation, "uncontrolled" as it may be termed by those who blindly adhere to a doctrinaire concept of the necessity for a "controlled" type of study, affords a more valid index for predicting the reaction of the population at large to the drug than a circumscribed "controlled" type of study performed by one investigator on the patients of his selection and with all of the limitations inherent in him and such a study.

It is of some interest, however, that the results of individual evaluations of choline salicylate, including controlled studies, have also been reported[24–26,29–31] and that the results of these conform in general to those reported here. All of these studies, including this report, appear to justify certain conclusions:

Choline salicylate is absorbed at a much more rapid rate than acetylsalicylic acid. It displays typical analgesic, anti-inflammatory, and antipyretic properties qualitatively resembling those of other salicylates. It undoubtedly induces considerably less gastrointestinal irritation than other salicylates and is better tolerated than acetylsalicylic acid in the population at large and can accordingly be administered to many patients in higher dosages than acetylsalicylic acid.

The results reported here clearly indicate not only that some patients will receive more benefit from and react more favorably to acetylsalicylic acid, but they also unequivocally demonstrate that more patients react more favorably to choline salicylate. Choline salicylate must therefore be considered equally with acetylsalicylic acid as a salicylate of choice in all patients and as the salicylate of choice in the many who will react more favorably to it than to aspirin. Indeed, the results of this study indicate the probability of a more favorable reaction to choline salicylate than to acetylsalicylic acid in any representative sample of patients, considered as a group. In actual practice the choice of a salicylate for any patient would appear to depend on his reaction to the drug. Certainly, if it appears that maximum benefit has not been obtained from use of acetylsalicylic acid or other salicylates, data reported here and elsewhere make a trial of treatment with choline salicylate almost mandatory. For obvious reasons, the greatest benefit from choline salicylate can be anticipated in those patients who can tolerate it in higher dosages than aspirin. Accordingly, the dosage of choline salicylate should always be increased to the highest that can be tolerated. For similar reasons, if the response to choline salicylate is not satisfactory, resort to trial with another salicylate would appear advisable. At the very least, choline salicylate provides the physician with another acceptable salicylate therapy.

In view of the clearly defined advantages of choline salicylate over acetylsalicylic acid (and other salicylates), it is of interest to discover the basis for these advantages. We are presently inclined to attribute these primarily to the drug's extreme solubility in water. A review of the available data strongly supports the thesis that the rate of absorption of salicylates is directly proportional to their solubility in water. An inverse correlation has been demonstrated to exist between solubility and induction of blood loss from the gastrointestinal tract. In other words, the amount of blood loss was in inverse proportion to the solubility in water.[28] Obviously, the extremely soluble choline salicylate would then be expected to be considerably less irritating to the gastrointestinal tract than the relatively insoluble acetylsalicylic acid.

The mechanism of the relationship between greater solubility and increased rate of absorption requires no lengthy explanation. Obviously, absorption occurs in the dissolved state. The relationship between solubility and lack of gastrointestinal irritation also seems straightforward. An irritant drug, in prolonged contact in high concentration with a sensitive mucosa as a result of its insolubility and slower rate of absorption, would appear more likely to induce greater irritation than a drug even with potentially similar irritant properties, but that, by virtue of its marked solubility and its extremely rapid rate of absorption through the musosa, is in contact with the same mucosa for a much shorter period of time.

SUMMARY AND CONCLUSIONS

The clinical pharmacology of the salicylates has been reviewed and it is emphasized that the previously available representatives of this valuable class of drugs possess certain undesirable properties.

The synthesis and properties of the new drug, choline salicylate, have been described. Choline salicylate has been made available as a water-soluble, stable, true solution.

The rate of absorption of equivalent doses of choline salicylate has been determined and compared to that of acetylsalicylic acid. Choline salicylate is absorbed five times as rapidly as acetylsalicylic acid and peak plasma salicylate levels are attained 12 times more rapidly after choline salicylate than after aspirin.

The clinical effects of choline salicylate were evaluated in a cooperative study by 80 physicians in more than 1200 patients and compared, as a reference standard, with those of acetylsalicylic acid.

Choline salicylate was demonstrated to possess typical analgesic, anti-inflammatory, and antipyretic effects qualitatively similar to those of other salicylates. Choline salicylate was more easily administered in large dosages than acetylsalicylic acid, particularly to infants and children and also to adults who experienced difficulty in swallowing tablets and capsules.

Choline salicylate was well tolerated. It induced a lower incidence of gastrointestinal distress, was less irritating to the gastrointestinal tract, and was tolerated in higher dosages than acetylsalicylic acid. These properties were particularly evident in patients with peptic ulcer and gastritis. These characteristics, as well as the drug's greater absorption, were attributed to its extreme solubility in water.

It is concluded that choline salicylate is a valuable agent. Choline salicylate was characterized as *a* salicylate of choice in all patients and *the* salicylate of choice in many. The probability of a more favorable reaction to choline salicylate than to acetylsalicylic acid can be predicted in any representative sample of patients considered as a group, if choline salicylate is used properly by administering it in the highest tolerated dosage.

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Choline Salicylate: A New and More Rapidly Absorbed Drug for Salicylate Therapy

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Salicylates, and acetylsalicylic acid in particular, are undeniably the most commonly used of all drugs, and attempts to improve them continue. There is a need for a stable soluble compound that can be administered in a palatable liquid to children and others who cannot swallow tablets. Acetylsalicylic acid is neither water soluble nor stable in aqueous suspension, and sodium salicylate in large dosages presents the problem of excessive intake of sodium ion, which may be undesirable in certain patients.

Aspirin does produce gastric irritation in a significant number of persons and has been indicted as the cause of mild and even severe gastric hemorrhage.[1] Attempts to buffer acetylsalicylic acid with sodium bicarbonate or nonsoluble antacids have not met with uniform success in alleviating or diminishing gastric distress.[2, 3] Whereas sodium bicarbonate may be more effective in this regard, it also increases the rate of urinary excretion of salicylate.[4, 5] Consequently, although salicylate may be absorbed more rapidly in its presence than when equivalent dosages are given without sodium bicarbonate, the salicylate blood levels so attained tend to drop very rapidly to a therapeutically ineffective level. It would appear, then, that the ideal salicylate should be one that produces minimal gastric irritation, is absorbed as well as or more rapidly than aspirin but yet maintains a relatively prolonged high blood salicylate level, and is ideally available also as a liquid. Choline salicylate,† a newly synthesized organic salt of salicylic acid, appears to offer promise of meeting most of these criteria.

Choline salicylate is a white (colorless) crystalline material, melting at 49.5 to 50.5 C. It is extremely soluble in water as well as alcohol, acetone, and similar water-miscible solvents. It has an empirical formula of $C_{12}H_{19}NO_4$ and a molecular weight of 241. It is the salt of the strongly basic choline ion and salicylic acid. As such, its aqueous solutions are stable and do not liberate free salicylic acid or choline on standing, and it exists in solution in the form of its dissociated ions. (See figure 1.)

Its aqueous solutions are colorless and odorless. Its extreme solubility in water permits preparation of wide ranges in concentrations. A 10 per cent solution of choline salicylate has a *p*H of 6.75 and does not liberate free salicylic acid until the *p*H is sharply decreased.[6] In view of these properties, it appeared appropriate to examine certain aspects of the drug's pharmacological activity in man.

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† The trade name of The Purdue Frederick Co. for choline salicylate is Arthropan. The drug was supplied for this study by this firm.

MATERIAL AND METHODS

The subjects used in this study were all adult men ranging in age from 30 to 60 years, who were hospitalized for a variety of diseases, mostly of a chronic nature. This report is not primarily concerned with observations on the therapeutic effects of choline salicylate.

During the earlier phases of our work, choline salicylate was administered in the form of a cherry-flavored solution, each teaspoonful of which (5 ml.) contained 435 mg. of drug. In all subsequent work, the drug was used in twice that concentration in the same vehicle, i.e., 870 mg./5 ml. As such, 1 teaspoonful provided the equivalent (in terms of salicylate content) of 325 or 650 mg. of aspirin, respectively. It was found most convenient to administer the drug directly from a medicine glass, a procedure that enabled the patient to ingest large doses with ease. For this reason, due to the method of calibration of medicine glasses, many of the doses employed were not exactly equal to or multiples of the conventionally accepted standard teaspoon (5 ml.). In order to prevent confusion, dosages of choline salicylate will be expressed in terms of weight of active drug administered, so that 87 mg. of choline salicylate is equivalent in salicylate content to 65 mg. aspirin.

Except where otherwise noted, salicylate blood levels were determined when the drugs had been given after an overnight fast and food was denied the patient until the completion of the tests. Salicylate content was determined by a modification of the procedure of Brodie, Udenfriend, and Coburn[7] and expressed in terms of mg./100 ml. plasma total salicylate.

RESULTS

Rate of Absorption of a Single Dose. This study was designed to establish the rate of absorption of choline salicylate and to compare its rapidity with that of acetylsalicylic acid. For this purpose, 9 patients were each given both drugs. Five received choline salicylate first and four days later were given aspirin; in the other 4, the order was reversed. Due to the method of calibration of the medicine glass, the dose of choline salicylate provided 926 mg. salicylic acid. Aspirin was given in the form of 4 commercial 325 mg. tablets, containing a total of 995 mg. salicylic acid, swallowed within a few seconds with the aid of a glass of water. Blood was drawn and plasma salicylate levels were determined before administration of the drugs and at 12, 30, and 60 minutes thereafter. The results of these determinations are tabulated in table I and they demonstrate the comparative rates of absorption of the two drugs.

It is readily seen that the plasma salicylate levels after choline salicylate were much higher than after aspirin at 12 minutes and higher also after both 20 and 60 minutes. In essence, these results confirm those of other workers who have reported that peak plasma salicylate levels may be attained as rapidly as 10 minutes after

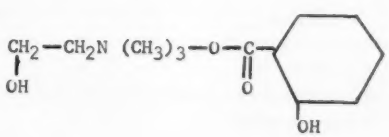

FIG. 1. Structural formula of choline salicylate.

TABLE I

Plasma Salicylate Levels (mg./100 ml.) After Oral Administration of 1.63 Gm. of Choline Salicylate (Equivalent to 18.7 gr. of Aspirin) and 20 gr. (1.3 Gm.) of Aspirin

	Time after administration					
	12 minutes		30 minutes		60 minutes	
Subject	Choline salicylate	Aspirin	Choline salicylate	Aspirin	Choline salicylate	Aspirin
A	6.75	2.0	7.50	2.00	6.75	2.00
B	3.75	0.25	5.25	2.50	8.00	3.75
C	3.25	0.25	5.25	1.50	4.75	2.25
D	8.25	0.25	10.75	6.25	9.50	9.00
E	3.75	0.25	6.75	2.00	6.75	4.75
F	0.25	2.25	1.25	4.75	3.25	6.75
G	1.75	2.75	2.50	6.25	6.00	8.00
H	4.50	3.00	9.50	4.75	12.00	7.00
I	7.00	2.25	8.25	6.25	9.25	5.75
Mean	4.37	1.47	6.33	4.03	7.36	5.47
Standard error	0.86	0.40	1.04	0.67	0.88	0.82

administration of a single dose of choline salicylate,[6] whereas peak levels are not attained until at least two hours after aspirin.[8]

When the data in table I were subjected to an analysis of variance (see table II), it readily became apparent that the main sources of variation between the blood level curves after the two drugs could be attributed not only to the different times

TABLE II

Analysis of Variance of Plasma Salicylate Levels in Table I

Source of variation	Degrees of freedom	Sum of squares	Mean square	Computed F
Main effects				
Among subjects	8	127.7176	15.9647	3.12*
Between drugs	1	75.2604	75.2604	14.73†
Among times	2	113.4190	56.7095	11.10†
First order interactions				
Subjects x drugs	8	41.7292	5.2162	1.02‡
Subjects x times	16	29.3519	1.8345	‡
Times x drugs	2	2.2709	1.1355	‡
Error	16	81.7707	5.1107	
Total	53			

* P <0.05.
† P <0.01.
‡ Not significant.

at which the levels were determined but also to the differences between the two drugs themselves. It is obvious that these differences are highly significant ($P < 0.01$).

The differences in salicylate levels after the two drugs at any fixed time were analyzed for their significance by conventional statistical procedures. At 12 minutes, the salicylate levels after choline salicylate were determined to be significantly higher than those after aspirin, these differences being significant at the 1 per cent level ($P < 0.01$). The observed differences in the means at 30 and 60 minutes could not be interpreted as statistically significant, although one might postulate that such significance between these differences could be established simply by a slight increase in size of the sample studied.

Figure 2 compares the blood levels attained in 3 representative patients. These curves are interesting, not only because they again, in an individual manner, demonstrate the better absorption of choline salicylate, but also because the curves resemble one another qualitatively, appearing to indicate that the patient who, for one reason or the other, absorbs aspirin well will do likewise with choline salicylate but at an even more rapid rate.

Salicylate Blood Levels During Prolonged Administration of Choline Salicylate. Having established the essential character of plasma salicylate levels during the early interval after ingestion of a single dose of choline salicylate, it became of interest to determine the course of such levels during daily administration, in divided doses. In order to determine this, choline salicylate in a dose of 1.63 Gm. (containing 926 mg. salicylic acid and equivalent to approximately 1.2 Gm. aspirin) was given four times daily to each of 9 patients for a period of 14 days. Plasma salicylate levels were determined at two hours after the noon dose on the seventh day, two hours before the first morning dose on the ninth day, two hours after the noon dose on the fourteenth day, and on the morning of the fifteenth day, 12 hours after the last dose had been given. Thus, the levels on the seventh and fourteenth days are somewhat comparable, each establishing values obtained two hours after the last preceding dose (an interval at which the blood levels are known to be declining after the peak values obtained

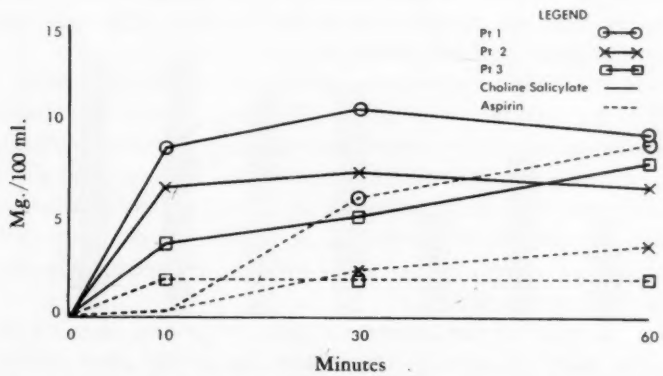

FIG. 2. Comparison of blood salicylate levels in the same 3 patients after equivalent oral doses of choline salicylate and acetylsalicylic acid.

TABLE III

Average Blood Salicylate Levels in mg./100 ml. in 9 Patients After 7, 9, 14, and 15 Days' Administration of Choline Salicylate (1.63 Gm. Four Times Daily)

7th day*	9th day†	14th day*	15th day†
15.27	9.20	14.54	10.50

* Two hours after last preceding dose.

† Twelve hours after last preceding dose.

after administration of a single dose). Similarly, the levels on the ninth and fifteenth days may be considered comparable since they represent residual salicylate levels some 12 hours after ingestion of the preceding dose. The results of these determinations are presented in table III.

In spite of the variations between individual patients, it seems apparent that this type of dosage regimen maintained fairly steady and satisfactory blood salicylate levels throughout the period of observation. Such results fail to reveal any tendency toward adaptation or any alteration in the method with which choline salicylate is handled. It is of interest also to note the salicylate levels determined on the ninth and fifteenth days. These indicate that appreciable quantities of salicylate remain in the blood as long as 12 hours after the last dose, and would appear to provide some assurance that a residual therapeutic effect might be maintained throughout the night even in the absence of "round-the-clock" administration of choline salicylate. At least, these levels provide a base from which much higher levels might be attained almost immediately after the first morning dose.

A somewhat similar procedure was used to compare the salicylate blood levels resulting from daily administration of choline salicylate and acetylsalicylic acid. In this case, the same dosage of choline salicylate as before, namely, 1.63 Gm. four times daily, was given for seven consecutive days to each of 4 patients and the plasma salicylate level was determined two hours after the midday dose on the seventh day. After a four-day rest, 1.3 Gm. of aspirin four times daily was then given to these same patients for another seven days and salicylate blood levels were again determined two hours after the midday dose on the last day. The same procedure was repeated in reverse order on 2 additional patients.

The results of this study are as follows: average blood salicylate levels after choline salicylate, 20.84 mg./100 ml.; after aspirin, 22.28 mg. These data demonstrate that essentially similar salicylate levels were maintained in this manner after both choline salicylate and aspirin. On the other hand, it should be noted that the daily dosage of choline salicylate required to maintain such levels was equivalent in salicylate content to only 90 per cent of the dosage of aspirin, for the total daily dosage of choline salicylate was equivalent to only 4.645 Gm. of aspirin, whereas 5.2 Gm. of aspirin was actually given each day.

Side Effects. In view of the known incidence of gastric bleeding after aspirin,[1] an attempt was made to estimate the occurrence of this after choline salicylate. The latter, in dosages equivalent to 650 mg. aspirin four times daily, was given to each of 20 patients for one week. None complained of any gastrointestinal distress,

but occasional occult blood was revealed in the stools of 3 of these as demonstrated by positive guaiac tests. When, after a rest, 650 mg. of aspirin four times daily was given to the same 20 patients for seven consecutive days, positive guaiac tests were demonstrated in the stools of 3 different patients, in whom occult blood in the stool had not been present during the administration of choline salicylate.

In another group of 7 patients an attempt was made to determine the maximum tolerance of choline salicylate. Choline salicylate was administered in doses of 870 mg. four times daily and the dosage was increased by 870 mg. four times daily until either nausea, vomiting, or other signs of toxicity developed. After a rest, aspirin was administered in doses of 650 mg. four times daily and the dosage was then increased by 2.6 Gm. daily until the appearance of symptoms that necessitated stopping the drug. The results of these trials are summarized graphically in figure 3 and demonstrate that some of the patients were able to tolerate almost double the quantity of salicylate in the form of choline salicylate as they could in the form of aspirin. Admittedly, although no valid conclusions may be drawn from such a small sample, these results appear to indicate that more salicylate may be given to some patients in the form of choline salicylate than could be tolerated in the form of aspirin.

Another type of problem was encountered in the long-term administration of large dosages of choline salicylate. Under such circumstances, after a period of several weeks, some patients complained of increasing distaste for the drug. At first, it was felt that this phenomenon might be attributed to the sirupy sweetness of the preparation. However, no such symptoms appeared when the vehicle itself was given in the form of a placebo and this phenomenon is apparently due to the drug itself. However, information received from others indicates that the frequency of this symptom can be minimized or dissipated by taking choline salicylate diluted in water and/or swallowing water after it. It is also reported that any residual aftertaste can be minimized by chewing gum or through use of a candied lozenge. Apparently neither of these complaints is encountered in children.

Patient Acceptance. It could be anticipated that the availability of choline salicylate as a pleasantly flavored liquid would render it very acceptable to infants and children

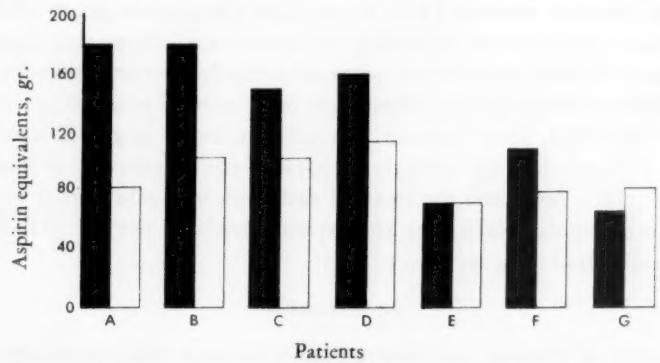

FIG. 3. Comparison of maximum tolerance to choline salicylate and aspirin in 7 patients. Black columns: Choline salicylate. White columns: Aspirin.

and such appears to be the case.[9, 10] However, we were able to note that it was also preferred to tablets of aspirin by many adults, particularly those who because of age or esophageal disease had difficulty in swallowing tablets. Many older patients are notoriously prone to gag on tablets, and they expressed preference for the liquid medication, particularly when they would have been required to swallow several tablets as a single dose. In general, however, the average adult who experienced no difficulties in swallowing tablets expressed preference for tablets of aspirin over choline salicylate.

DISCUSSION

Because of the difficulty in obtaining unequivocal evidence of the ability of salicylates to reduce pain of moderate severity either in animals or in normal human subjects, inadequate data are available to determine the salicylate blood level required to achieve analgesia.[11] In rheumatic fever, a concentration of 25 mg./100 ml. seems to be necessary for the desired anti-inflammatory effect, whereas 30 to 45 mg./100 ml. is considered optimal.[12] In rheumatoid arthritis, it would appear that the most effective results can be obtained from the maximal dosage that can be tolerated.

These considerations are of some importance in evaluating the data presented in this study. For, despite the lack of knowledge as to the salicylate blood levels required to achieve certain effects, it would seem probable that the more rapidly a high blood level could be attained, the more rapid would be the relief appreciated by the patient. Our results and those of others appear to establish that higher blood levels are attained much more rapidly after single doses of choline salicylate than after aspirin. Accordingly, in the treatment of acute episodes such as headache, etc., it seems plausible that relief should be afforded more rapidly after a dose of choline salicylate than after aspirin if the analgesic activity is a function of the salicylate blood level.

Our results also demonstrate that choline salicylate can maintain apparently adequate therapeutic blood salicylate levels during long-term administration of the drug and that these high levels, after administration of both single or repeated doses, can readily be achieved without any undue amount of gastric distress.

Admittedly, the data presented here in regard to the relative degree of tolerance to choline salicylate as compared to aspirin are inadequate. However, after more than a year of experience with choline salicylate, it is our definite impression that average dosages of choline salicylate are tolerated at least as well as aspirin. Moreover, as we have demonstrated, some patients can tolerate much larger dosages of choline salicylate than of aspirin. Accordingly, in view of the importance of high salicylate dosage in rheumatic fever and rheumatoid arthritis, it would appear that the drug of choice between choline salicylate and aspirin should be the one that is best tolerated by the individual patient.

CONCLUSIONS

1. Single doses of choline salicylate are absorbed at a much more rapid rate than aspirin. It is suggested that the former should therefore afford relief, in the form of analgesia, in acute episodes more rapidly than aspirin.

2. Adequate therapeutic blood salicylate levels can be maintained during prolonged administration of choline salicylate.

3. When choline salicylate is given in divided doses during the day, significant and appreciable salicylate blood levels are present the next morning, 12 hours after the preceding dose.

4. Choline salicylate appears to be at least as well tolerated as aspirin. Average and even larger dosages do not appear to induce an undue incidence of gastric distress. Some patients tolerate much more salicylate in the form of choline salicylate than aspirin.

5. Choline salicylate, a medication available in liquid form, presents definite advantages over aspirin for salicylate therapy in infants, children, and adults who have difficulty in swallowing aspirin.

6. Choline salicylate appears to be an important and valuable contribution and undoubtedly deserves further study and use.

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Observations on the Usefulness of a New Liquid Salicylate in Arthritis

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Of the numerous agents introduced for therapy of rheumatoid arthritis, few have withstood the test of time. In this, as in other chronic remitting diseases of variable course, a host of remedies have been tried and discarded because of ineffectiveness or toxicity. It is generally conceded today that optimal long-term results are best achieved by thoughtful and individualized programs. These programs entail careful follow-up observations guided by adequate records; advice as to adaptation of living according to activity of disease; avoidance of physical and emotional fatigue; physiotherapy with emphasis on planned exercises; protective splints, casts, and, where indicated, orthopedic procedures. These general measures are supplemented by one or more of the handful of drugs currently in vogue that show, or are purported to show, antirheumatic effects.

The list of drugs currently used in rheumatoid arthritis is small. It includes gold, phenylbutazone, certain antimalarial compounds, steroids, and salicylates. All these compounds may induce serious toxic manifestations. The least toxic of all are the salicylates, and few physicians experienced in the management of patients with rheumatoid arthritis would dispute their value. Indeed the majority lean heavily on salicylates in some form, turning to the other preparations only when conservative programs have clearly failed.

Salicylates are time-honored remedies. Only very few drugs, such as opiates, can compare with them in duration of use. The glycoside salicin was isolated by Le-Roux[1] in 1827. The first documented demonstration that salicylates enjoy potent anti-inflammatory properties was by Maclagan in 1876,[2] who gave them to patients with rheumatic fever. Acetylsalicylic acid was synthesized in 1853 by von Gerhardt and introduced into medical practice in 1899 by Dresner,[3] and since then aspirin has held undisputed sway as the most widely used of all drugs. A number of other salicylates are presently available, yet because of untoward effects, the search for safer, more rapidly absorbed, and less irritant modifications continues. These modifications have included protective coatings, combinations with "buffers," and chemical alterations of the molecule. For optimal results in rheumatoid arthritis, all salicylates should be given in the maximum dosage tolerated by the individual patient. Whereas many persons can tolerate continued salicylate medication without distress, gastrointestinal symptoms do appear in a large percentage. Usually these symptoms are mild, though a more serious problem is that of bleeding from the

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gastrointestinal tract.[4] In an attempt to avoid such side effects, buffered aspirin[5] has been advocated, but its relative value has been seriously questioned.[6] Enteric coating of aspirin has been helpful,[7] but patients frequently fail to absorb the drug and pass the tablets in the stool. The coating does not always avoid the problem of occult bleeding.[8] Sodium salicylate may cause less occult bleeding, but it is not always well tolerated, and under certain conditions the sodium ion is undesirable.

Recently, a newly developed salicylate, choline salicylate,* has been introduced. Choline salicylate is water soluble and stable in aqueous solution without liberating free salicylic acid or choline. It has been shown to be nontoxic in therapeutic dosage.[9] It has been introduced as an alternative form for administration of salicylates with the possibility of certain advantages in the following circumstances: in the treatment of patients who have difficulty in swallowing or dislike taking tablets, for example, children and elderly persons; where rapid absorption is important; where other salicylates are poorly tolerated; where intake of sodium ion is undesirable.

We have had an opportunity to observe the effects of the administration of choline salicylate and wish to report our observations here.

METHODS AND MATERIAL

Choline salicylate was studied from the points of view of taste tolerance, gastric distress, speed of absorption, analgesic effects, anti-inflammatory properties, and hypersensitivity. It was administered to 14 normal subjects and to 50 patients. Of these patients, 20 were given one or more doses for a variety of minor painful disorders such as headache, toothache, menstrual cramps, and acute bursitis. The drug was also given to 30 patients with chronic arthritis. Of these, 20 had active rheumatoid arthritis and 10 had osteoarthritis. In these cases, the drug was administered three or four times daily for periods ranging from two weeks to 10 months, with an average of 43 days. Patients with rheumatoid arthritis conformed to the American Rheumatism Association's proposed diagnostic criteria.[10] Ages ranged from 3 to 79 years. Since most patients given continuous medication had previously been taking aspirin, choline salicylate was started in equivalent dosage and increased according to tolerance. Maintenance dosages varied from 35 to 55 ml./day (equivalent in salicylate content to 70 to 110 gr. of aspirin), with an average of 40 ml. of choline salicylate. Blood salicylate levels were estimated according to the method of Keller.[11]

RESULTS

Short-Term Analgesia. The 20 patients studied from this point of view were given 5 or 10 ml. of choline salicylate. By the crude subjective criteria available to evaluate analgesia, no definite difference in speed of pain relief could be demonstrated in comparison with equivalent amounts of aspirin.

Notwithstanding, the total serum salicylate levels in a series of rheumatoid pa-

* The trade name of The Purdue Frederick Co. for choline salicylate is Arthropan. The drug is available in the form of a cherry-flavored aqueous solution, each teaspoon (5 ml.) containing 870 mg. of choline salicylate, equivalent to 10 gr. (650 mg.) of aspirin.

TABLE I

Total Serum Salicylate Levels (mg./100 ml.) in 11 Paired and 3 Other Subjects (See Text) After Oral Administration of Equivalent Amounts (1 Gm. of Salicylate) of Choline Salicylate and Acetylsalicylic Acid

Pair or subject	Time after administration					
	10 minutes		30 minutes		60 minutes	
	Choline salicylate	Aspirin	Choline salicylate	Aspirin	Choline salicylate	Aspirin
1*	9.8	0.2	13.0	0.2	15.0	1.4
2*	6.0	0.2	7.6	0.2	9.1	1.7
3*	9.2	0.2	13.8	1.4	12.1	4.7
4*	11.6	0.2	14.2	0.7	13.1	4.0
5*	12.0†	4.4†	12.2	5.1	10.8	6.0
6	13.5†	0.2	9.0	0.2	8.8	1.4
7	1.2†	0.2	4.0	5.8	9.0	1.7
8	3.7	4.7†	7.6	5.5	12.5	9.4
9	6.3†	0.2	11.8	1.4	13.7	0.5
10	14.3	0.8†	20.0	1.0	13.2	2.2
11	11.8	0.7†	14.2	8.6	13.1	6.0
12	10.3		13.0		14.0	
13	6.3		10.9		8.6	
14	10.0†		16.0		22.0	
Mean	9.0	1.1	11.7	2.7	12.4	3.5

* These subjects received both drugs.

† Patient with diagnosis of rheumatoid arthritis. All others were normal volunteers.

tients and normal volunteers were significantly higher after choline salicylate than after an equivalent quantity of aspirin (see table I). In each instance the drug was given in the fasting state with 100 ml. of water. In this group, 5 subjects first received one and then the other drug. None had received salicylates for at least three days prior to the administration of either drug. Blood levels were determined at 10, 30, and 60 minutes after ingestion of either drug.

It is seen in table I that 10 minutes after the administration of 10 ml. of choline salicylate, the mean salicylate blood level was approximately 9 mg./100 ml. and that a peak level of about 12 mg./100 ml. was reached in 30 minutes. On the other hand, when an equal amount of salicylate was given in the form of aspirin, the mean blood level had reached only 3.5 mg./100 ml. at the end of 60 minutes. Comparing the mean levels, it is evident that choline salicylate is absorbed much more rapidly than aspirin. The relative blood salicylate levels after choline salicylate and aspirin exceed 8:1 in 10 minutes, 4:1 in 30 minutes, and 3:1 in 60 minutes.

In attempting to assess the significance of these differences, the subjects from whom the blood level data were derived were considered as comprising two groups: The first of these consisted of the 5 subjects in whom levels were determined after both choline salicylate and aspirin. Although this number is quite small, it is a

definitive group since, by serving in the form of a crossover, the subjects acted as their own controls. The second group consisted of all the subjects in this test: the afore-mentioned 5 plus another 12 in whom the levels had been determined after only one of the two drugs, plus another 3 in whom levels were determined only after choline salicylate. This latter group thus presented results from "paired" determinations in a group of 11, of whom both members of 5 pairs were actually the same persons.

The data were first subjected to an analysis of variance, with three principal sources of variation (among subjects, among times at which the blood levels were determined, and between the two drugs). It is of extreme interest that, in both groups, the difference between the two drugs was found to contribute to the greatest degree to the differences between the mean levels for all subjects, at all times, such differences having been determined as extremely significant ($P < 0.001$).

When the differences between the mean total salicylate levels at any fixed time were evaluated, similar significance was demonstrable. Thus, even in the very small crossover group of 5, the mean levels after choline salicylate were found to be significantly higher than after aspirin ($P < 0.05$), at each of the 10-, 30-, and 60-minute intervals. When the entire group was considered, these differences were found to be even more significant ($P < 0.01$ at 10 and 30 minutes and $P < 0.001$ at 60 minutes). Thus, the rate of absorption of choline salicylate is so much more rapid than that of acetylsalicylic acid that this difference is readily demonstrable in even a very small group of 5. These findings readily confirm previous somewhat similar reports on the much more rapid absorption of choline salicylate in both normal subjects and patients.[9, 12]

Long-Term Administration. The 30 patients with chronic arthritis to whom choline salicylate was administered in continuous dosage varied widely in their acceptance of and tolerance to the drug. Nineteen patients obtained continuous satisfactory control of pain and stiffness without any side effects. Those who first complained of an unpleasant taste found that this could be minimized by adequate dilution with water and by rinsing the mouth. Of these, 12 or 40 per cent of the entire group of 30 preferred choline salicylate to previously used salicylates, and 7 expressed no preference. Eleven patients complained of the taste. Three of these developed nausea and vomiting. Six refused further medication; 3 because of nausea and taste, 2 because of nausea, vomiting and taste, and 1 because of taste. Maximum tolerance was determined in 7 adults and found to be in the range of 35 to 65 ml. (equivalent in salicylate content to 70 to 130 gr. of aspirin per day) before symptoms of salicylism appeared. Tolerance varied usually but not always according to body weight. Random blood salicylate levels in this group correlated anti-inflammatory and analgesic responses with effective levels. These were usually between 20 and 25 mg./100 ml.

Antirheumatic Effect. In order to demonstrate anti-inflammatory and antirheumatic properties in the rheumatoid group, 5 patients with active rheumatoid arthritis were studied for quantitation of activity of disease by a previously proposed method. These patients, with one exception, a woman who was experiencing a severe and prolonged exacerbation, showed definite reduction of the "systemic indexes," de-

TABLE II

"Systemic Indexes" During Continuous Administration of Choline Salicylate in Optimal Dosage, by the Simplified Method of Wallace and Ragan

Patient	Dose per day, ml.	Initial systemic index	After 2 weeks	After 4 weeks
J. M.	20	4	3	0
D. B.	40	15	12	6
M. D.	40	6	11	9
E. F.	20	12	10	8
M. G.	20	8	6	4

scribed by Wallace and Ragan.[13] As is indicated in table II, improvement was already manifested at the end of two weeks and a very significant reduction in the "systemic indices" was noted in 4 cases at the end of four weeks, although 3 of these patients received dosages equivalent to only 40 gr. of aspirin per day.

Hypersensitivity. It is not known whether patients allergic to acetylsalicylic acid are hypersensitive to the whole molecule or the acetyl radical.[14] Choline salicylate was tested cautiously in 3 patients who had had repeated allergic reactions to aspirin. Two of these had manifested severe asthmatic attacks after the ingestion of aspirin. The third had fever and urticaria. It was found that all 3 tolerated repeated and prolonged medication with choline salicylate. These observations suggest that some persons may be sensitive only to the acetyl portion of the aspirin molecule and suggest a possible additional use for choline salicylate in sensitized patients in whom salicylates are indicated. In testing hypersensitive subjects it is essential that the initial challenge be made with extreme caution and the patient be kept under close observation for at least one hour.

SUMMARY AND CONCLUSIONS

The present status of therapy in rheumatoid arthritis is reviewed. The basic role of salicylates is emphasized and different preparations are discussed with comments on dosage and tolerance.

Data are presented on the use of the newly introduced stable liquid, choline salicylate. Studies showed a much more rapid rise in serum salicylate levels after choline salicylate than after comparable dosages of aspirin. The anti-inflammatory effectiveness of choline salicylate was demonstrated by the use of the "systemic index," as described by Wallace and Ragan. Forty per cent of the patients with chronic arthritis who were treated with choline salicylate expressed a preference for it over previously used salicylates. Three patients known to be hypersensitive to acetylsalicylic acid tolerated repeated and prolonged dosage with choline salicylate. Experience on the whole was favorable and this drug is recommended for treatment of arthritis and particularly when previously used salicylates were poorly tolerated, where a liquid preparation is preferred to tablets, where sodium intake is unde-

sirable, and possibly where patients in need of salicylate therapy are allergic to aspirin.

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FDA Criticizes Vitamin E Claims

The U. S. Food and Drug Administration has issued a statement denouncing extravagant therapeutic claims made for several vitamin E preparations that are being sold directly to the public. FDA said that although vitamin E is essential in human nutrition, it is so plentiful in foods that supplemental sources are both expensive and unnecessary. Claims that vitamin E will prevent and cure sterility, heart disease, and muscular dystrophy are false, according to the announcement.

Comparative Evaluation of the Effectiveness of Choline Salicylate in Treatment of Arthritis and Allied Conditions

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INTRODUCTION

Salicylates play an indispensable role in the treatment of the various types of arthritis. Even the advent of the steroids has failed to displace the salicylates from their position as the basic drugs of choice for the long-term and routine treatment of the more common varieties of chronic joint disease and rheumatic fever. Since it appears to have been established that no steroid can provide beneficial effects in a dosage low enough to avoid potentially serious side effects,[1] and since phenylbutazone is potentially toxic, these newer agents must be regarded as indicated for adjunctive therapy and for use for short periods only.

Nevertheless, it must be admitted that salicylates themselves suffer from certain inherent limitations. Thus, although they are relatively nontoxic, large dosages do induce systemic toxicity and they must necessarily be given in dosages below that level at which salicylism occurs. Yet, although it is admitted that maximum benefit from salicylate therapy is best obtained from those dosages just below those that evoke symptoms of salicylism, in actual practice it is not feasible to administer such high dosages to a large proportion of the population since gastrointestinal distress is evoked by dosages of a considerably lower magnitude. The experience of almost any rheumatologist will amply confirm the fact that a substantial percentage of arthritic persons cannot tolerate, without gastric distress, the chronic daily administration of dosages of acetylsalicylic acid or sodium salicylate in excess of 40 gr. Consequently, such patients are denied the theoretical maximum potential benefit from these drugs.

Acetylsalicylic acid appears to be particularly irritating to the gastric mucosa as evidenced not only by the frequency with which it induces symptoms of gastric distress but also by direct observation of its erosive effects.[2] Furthermore, an increasing amount of data has indicted it as a cause of both occult and frank gastric hemorrhage.[3] For such reasons and since, in our own experience, aspirin has appeared to produce a less lasting therapeutic effect than sodium salicylate, we have favored the use of the latter. Yet sodium salicylate is also inclined to induce gastric upsets in many patients and it has, therefore, been frequently administered in enteric-coated form, although such a practice obviously renders absorption somewhat haphazard.[4] Moreover, it must be admitted that the administration of large quantities of sodium-containing drugs may be inadvisable in certain groups of patients.

In addition to these drawbacks, a more serious problem is posed by those patients who cannot tolerate salicylates in any form, in any dosage. On occasion, such in-

tolerance may be due to an unusually low threshold to gastric distress. In others, the intolerance is undoubtedly the result of a true hypersensitivity as manifested by severe episodes of asthma or urticaria.

Consequently, it would appear highly desirable to have available a salicylate that could be given with impunity and elicit the desired therapeutic effect, at least in those patients unable to tolerate acetylsalicylic acid or sodium salicylate or in whom tolerated dosages of the latter fail to produce satisfactory relief. Recently, a new drug, choline salicylate,* has been described that appears to possess certain highly desirable properties. In contrast to aspirin, it is quite stable in true aqueous solution and would, therefore, appear ideally adapted for administration to children as well as those adults who, for various reasons, have difficulty in swallowing tablets. Choline salicylate has been demonstrated to be absorbed at an extremely rapid rate, peak plasma salicylate levels being attained after 10 minutes[5, 6] in contrast to the more than two hours required for similar levels after equivalent doses of aspirin.[7] Of even greater interest is the fact that although choline salicylate apparently possesses all of the desirable antipyretic, analgesic, and anti-inflammatory properties of other salicylates, it appears to be better tolerated than the latter, at least in a significant proportion of patients.[5]

In view of the several facts just enumerated, we considered it of sufficient interest to study the effects of choline salicylate in a series of our own patients. It is the purpose of this report to describe the results of our observations, which essentially confirm those already cited.

MATERIAL AND METHODS

Of the total number of patients to whom choline salicylate was given, its effects could be critically examined in a series of 45 who were observed closely and for a sufficient period. Forty-two of these were female patients and 3 were male patients; all were adults except 1 18-month-old girl with acute rheumatic fever. The diagnoses were established by conventional criteria including the required laboratory and roentgenographic procedures, and these are listed in table I.

In order to obtain a critical comparison between the effects of choline salicylate and other drugs, we included in our series 36 patients to whom other salicylates had previously been given and in whom the effects of these other salicylates had already been determined. Each of these 36 served as his own control in evaluating his response to choline salicylate in terms of the responses to the previous medication. Six of this group had previously exhibited a well-defined inability to tolerate other salicylates and were purposely included in the present study in order to obtain a more critical demonstration of any differences between the incidence of side effects with the various salicylates.

After the other medication had been withdrawn from those patients to whom salicylates had previously been given, choline salicylate was administered in the form of a flavored solution, each teaspoonful (5 ml.) of which contained 870 mg.,

* The trade name of The Purdue Frederick Co. for choline salicylate is Arthropan.

TABLE I

Summary of Results Obtained by Treatment with Choline Salicylate

Diagnosis of patients	Response of patients			
			Poor	
	Excellent	Good	Ineffective but well tolerated	Ineffective with side effects
Osteoarthritis	11	4	3	2
Rheumatoid arthritis	4		2	2
Mixed arthritis		1	1	1
Psoriatic arthritis	1		1	
Rheumatic fever	6			
Neuritis	1			1
Bursitis	1			
Osteoporosis	1			1
Acute toxic state		1		
Total	25	6	7	7

equivalent in salicylate content to 10 gr. of acetylsalicylic acid. Although it appears to be well substantiated that many patients tolerate much larger dosages,[8] we purposely prescribed it to the adults at a dosage level of 4 teaspoonfuls/day in divided doses. This limitation was imposed since, as was noted previously, a daily dosage of 40 gr. appears to be the maximum tolerated dosage for most patients in the case of sodium salicylate and acetylsalicylic acid. Accordingly, in order to compare the effects of the three drugs more critically, it was considered advisable to administer all in comparable dosages. The 18-month-old infant was treated with 60 drops/day, representing the equivalent of approximately 10 gr. of aspirin. All patients were observed periodically, at frequent intervals, to determine the status of their disease and symptoms.

Therapeutic results were graded as "excellent" if effective relief of symptoms was achieved, "good" if a moderate degree of relief was maintained or if satisfactory relief was obtained during part but not the entire period of observation, and "poor" if the degree of relief was considered unsatisfactory. In all instances, careful notation was made of any side effects.

RESULTS

Seven of the patients were treated and observed for periods of from a minimum of three days to less than a month, either because of the intervention of undesirable side effects or because the patients appeared to receive little benefit from the medication. The remaining 38 were treated and observed for periods of from one to more than eight months.

The over-all therapeutic effectiveness of choline salicylate is summarized in table I. It is apparent that 31 (69 per cent) of the patients received an appreciable degree

of relief from their symptoms, with the results being classified as excellent in 25 and moderate in 6. The relief of pain and the anti-inflammatory effects achieved in the successful cases were dramatic. These effects were obtained soon after therapy was initiated, thus appearing to confirm previous reports concerning the rapidity of absorption of the drug and the maintenance of therapeutically effective blood levels.

The results were graded as poor in 14 patients, either because insufficient relief was obtained or because side effects rendered continuation of treatment inadvisable. As will be noted later, the prescribed dosage was very well tolerated in 7 of these, and in 3 of the others, the patients complained of side effects of a nature and intensity insufficient, in our opinion, to have precluded trial of a large dosage.

Although 8 of the patients offered complaints referable to the drug, in only 5 of these were the side effects considered sufficiently severe in themselves to warrant discontinuance of further medication. Two of these patients developed symptoms of salicylism, as manifested by tinnitus and impairment of hearing, undoubtedly reflecting the excellent absorption of the drug into the blood. Three patients complained of gastrointestinal distress, 1 after three days and 2 after one month of therapy. These side effects were considered distressing enough to warrant withdrawal of the drug, though 1 of the latter 2 patients was receiving very satisfactory relief from the presenting complaints. Two patients offered complaints of the taste of the preparation and another, treated for three months, reported a vague and ill-defined slight "indigestion." Although the complaints of none of these latter 3 were considered severe enough in themselves to warrant discontinuance of choline salicylate, its administration was stopped, in deference to the patients, since they had not received satisfactory relief.

Of somewhat greater interest than these findings were the comparative reactions of the patients to choline salicylate and other salicylates. As has been noted, 36 of the 45 patients had previously been treated with a variety of salicylates, including combinations such as Pabalate and APC, and the results that had been obtained with these other medications were known and accurately defined. Accordingly, it became apparent that in this series of 36, treated with equivalent dosages of the several medications, choline salicylate proved definitely more effective in 16 or 44 per cent and was equally as effective (or ineffective) in 17. One or more of the other salicylates appeared to provide more effective relief in 3 of this group.

The comparison of the tolerance to the various drugs was also revealing. Six of the 36 patients tolerated choline salicylate better than the other salicylates. Fifteen tolerated both to the same degree, and other salicylates were better tolerated by 5. Of particular interest is the fact that choline salicylate was well tolerated in all 6 of the patients who previously had been unable to tolerate any other salicylate to any degree, for a variety of reasons including, in 1 case, dermatitis venenata. Since choline salicylate provided very effective relief in 4 of these patients, the latter were able for the first time to receive the full benefit of salicylate therapy.

Analysis of these results indicates that choline salicylate was more effective and/or better tolerated in 18 or 50 per cent of the patients who received both it and other salicylates. Other salicylates were more effective and/or better tolerated in 7.

DISCUSSION

The results just reported are in excellent agreement with those of others[9–11] who have reported choline salicylate as an effective anti-inflammatory and analgesic agent, which satisfies the recognized need for a salicylate with a high degree of effectiveness, a high degree of tolerance, and a low incidence of side effects. In our experience, the over-all degree of effectiveness (approximately 70 per cent) provided by choline salicylate represents the maximum that can be anticipated from the use of any salicylate in the treatment of these difficult and frequently intractable conditions.

However, it may also be pointed out, as has previously been indicated, that we purposely restricted our daily dosage to a maximum of 4 teaspoonfuls, in order to obtain a more valid assessment of the drug in comparison with other salicylates. This was done since our previous experience, in common with that of many others, revealed that most patients with arthritis cannot tolerate the prolonged administration of salicylates at a daily dosage in excess of 40 gr. Accordingly, in that group of patients who tolerated well the daily dosage of 4 teaspoonfuls of choline salicylate but who failed to receive sufficient benefit from it, the dosage was not increased in an effort to determine whether effective relief could be obtained from a higher dosage at a level at which side effects would still be absent. It is, of course, conceivable that such could have been the case, and inasmuch as others have since reported that many patients tolerate much larger dosages, we plan in the future to increase the dosage cautiously whenever that previously used has failed to provide the necessary degree of relief.

Although theoretical considerations might indicate that equivalent effects should be obtained from equivalent amounts of salicylate in the blood or tissues, regardless of the identity of the salicylate used to introduce it into the blood stream, there is no valid reason to postulate that all salicylates should produce similar effects if given by mouth. Thus, as we have indicated previously, we appear to have obtained more satisfactory long-term results from sodium salicylate than from aspirin. One salicylate may be so poorly tolerated due to gastrointestinal distress as to preclude its use in therapeutically effective dosages in a significant number of patients. Other salicylates, particularly when given as enteric-coated tablets, may be absorbed too slowly or too poorly to be able to provide a satisfactory degree and promptness of relief. The use of other salicylates may be prohibited by allergic manifestations or by undesirable or toxic effects from the nonsalicylate moiety. At any rate, apart from all academic considerations, these results confirm with certainty the fact that the properties of choline salicylate are such as to render its effects quantitatively different at least from those of other salicylates in a very appreciable percentage of patients. In many of this series of patients, choline salicylate has been demonstrated to be either more effective or better tolerated, at equivalent dosages, than any other salicylate previously used and, therefore, must be considered the salicylate of choice for these particular patients.

This does not imply that choline salicylate is to be considered the salicylate of choice for all patients. Indeed, as has been demonstrated, the results from other

salicylates were more satisfactory in a small number of patients and equally satisfactory in others. However, the results do indicate that, in initiating salicylate therapy, the choice of choline salicylate should be considered equally with all other salicylates. Furthermore, and more important, our results clearly demonstrate that choline salicylate is indicated in and its use should be tested in every patient in whom completely satisfactory results have not previously been obtained with the use of other salicylates. In other words, it appears that choline salicylate may be recommended whenever salicylates are indicated and its administration may enable the patient to achieve a degree of relief previously denied to him.

It is interesting to speculate as to the reasons why choline salicylate was found to yield better results in so many patients. Undoubtedly, the demonstrated much greater rapidity of its rate of absorption as compared to other salicylates and the maintenance of its blood levels over a prolonged period of time may well contribute to the promptness with which it appears to act. We are inclined to feel also that its extreme solubility may explain why it is well tolerated. Recently, an increasing amount of evidence has indicated that the more poorly soluble and slowly absorbed salicylate tablets, aspirin in particular, may produce an actual erosive effect on the gastric mucosa.[2] Since choline salicylate is absorbed so rapidly, no single area of the mucosa may ever be exposed for any appreciable time to a sufficient concentration of salicylate to induce irritation when moderate dosages of choline salicylate are ingested. At any rate, as a liquid, it was easily administered to the 1 infant in this series as well as to the adults.

SUMMARY AND CONCLUSIONS

Choline salicylate, in a dosage of 4 teaspoonfuls/day in adults and 60 drops/day in an infant, was administered for periods up to more than eight months to 45 patients with various types of arthritis and similar conditions. The drug was easily administered, well accepted, and well tolerated. During this prolonged period, it was found necessary to discontinue its use due to side effects in only 5 patients—in 2 because of salicylism and in the other 3 because of gastric complaints.

Choline salicylate provided an excellent or moderate degree of relief from the presenting symptoms in 31 (69 per cent) patients of the series.

Its effects were compared with those of other salicylates in 36 patients in whom their reactions to the latter were clearly established. Choline salicylate was more effective and/or better tolerated than other salicylates in 18 of these 36. Choline salicylate was well tolerated by all of 6 who previously had been unable to tolerate salicylates in any form. Other salicylates were more effective and/or better tolerated than choline salicylate in only 7 of the 36.

Choline salicylate is an effective, well tolerated, anti-inflammatory, and analgesic agent. Experience to date indicates that it may be recommended as a salicylate of choice for the treatment of arthritis and allied conditions. Choline salicylate may be the salicylate of choice in many patients with arthritis, and its effects should be tried in every patient in whom other salicylates have failed to provide entirely satisfactory results.

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Preliminary Observations on the Effective Use of Choline Salicylate as a Rapidly Acting, Well-Tolerated Analgesic Agent

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Although the mechanism of their pain-relieving action has not been clarified, the salicylates are the most widely used of all drugs for this purpose. Unfortunately, most available salicylates demonstrate certain undesirable properties. The frequent gastrointestinal distress and the sometimes frank hemorrhage that may be induced by aspirin[1] often prevent its use to the limit of its therapeutic potential. Large dosages of sodium salicylate are usually contraindicated in many patients in whom the intake of sodium should be restricted.

It has been stated that choline salicylate,* only recently made available, provides the medical profession with a salicylate without many of the disadvantages of the older drugs. A sodium-free molecule, it is, unlike aspirin, extremely soluble in water and may be administered as a stable, true solution.[1] It has repeatedly been demonstrated to be absorbed at least five times as rapidly as acetylsalicylic acid[1–6] and to induce peak plasma salicylate levels as early as 10 minutes after ingestion,[1, 2] as contrasted with the more than two hours required after aspirin.[7] Although therapeutic blood levels are thus attained so much more rapidly, they are equally well maintained for as long a period as after acetylsalicylic acid.[1, 2] Several investigators have also maintained that choline salicylate induces a much lower incidence of gastric distress, and it is said to be better tolerated than aspirin in many patients.[1, 2, 4, 8, 9]

The rapidity of its absorption would appear to imply a more rapid onset of its action and such a property would appear to be of particular benefit in acute situations where the earliest possible relief from pain is desirable. In fact, significant reduction in temperature and relief of malaise in postimmunization reactions in infants has already been demonstrated to occur as early as 10 minutes after ingestion of choline salicylate.[10] In view of such data and the various reports of the drug's clinical effectiveness and relative freedom from side reactions in treatment of a variety of chronic conditions,[5, 8, 9, 11] this present study was undertaken to obtain a preliminary evaluation of use of the drug as an analgesic agent in acute episodes of short duration.

MATERIAL AND METHODS

Fifty patients were included in this study. Forty-seven were more than 20 years of age, 2 were adolescents, and 1 was an infant. The average age of the 47 adults was

* The trade name of The Purdue Frederick Co. for choline salicylate is Arthropan.

42 years and this group included 27 men and 20 women. The 2 adolescents and the 1 infant were girls.

Twenty-eight patients complained of headache. Of these 28, 25 (including 1 female adolescent) were diagnosed as having tension headache; 4 of these had other conditions that may have had some etiological relation to the presenting complaint. In addition, in 2 cases, the headache was part of a postconcussion syndrome, and 1 patient developed headache as part of a postimmunization reaction. Fifteen patients (13 adults, 1 adolescent, and 1 child) had infections of the upper respiratory tract with complaints of fever and generalized malaise, complicated in 1 instance with pleurisy. Three patients complained of severe pain due to lumbosacral strain. One had bursitis of the right shoulder; 1, neuritis of the right arm of unknown etiology; 1, a painful gastroenteritis; and 1, osteoarthritis of the cervical spine. This latter patient also had an active duodenal ulcer.

Choline salicylate was administered in the form of a cherry-flavored solution, each teaspoonful containing 870 mg., the equivalent in salicylate content of 10 gr. (650 mg.) of acetylsalicylic acid. Except in 3 cases, 1 teaspoonful was given, followed by 1 teaspoonful every four hours as required. A 4-year-old girl with grippe received ½ teaspoonful every four hours; the patient with pleurisy received 1 teaspoonful four times a day; and the oldest patient (aged 75), who complained of very severe headaches, received 2 teaspoonfuls every four hours.

Since, in the great majority of the cases, the symptoms and the related conditions were acute and of short duration, there was no need for extended therapy. The number of doses given in these cases varied from 1 to 10. The patient with pleurisy, who developed left pleuritic pain after acute bronchitis, was treated for nine days. More extended therapy was required in the case of a 50-year-old male patient whose chronic frontal headache complaints were part of postconcussion syndrome, and he was treated for 30 days. Twenty-two doses were sufficient (with simultaneously administered prednisone, 5 mg. four times daily) to eliminate all symptoms of neuritis in the right arm of a 56-year-old female patient.

With the exception of a few patients, the first dose of the preparation was administered in the office in order to record the time of the onset of action. All other patients were instructed to keep records of the time that elapsed between administration of the first dose and onset of effective action as well as the duration of relief from pain. Each patient was examined to detect any evidence of sensitivity or allergy and was questioned concerning other side effects, acceptability, and his opinion of the comparative properties of choline salicylate and aspirin.

RESULTS

In order to facilitate the evaluation of the effectiveness of the analgesic (and in some cases antipyretic) activities of the drug, the data were considered in two parts. The first pertained to the 28 cases of headache. Of these 28 patients, 25 (89 per cent) reported complete relief of pain. Of the 3 who failed to obtain relief, 1 patient reported subsequent relief with either aspirin or APC and 1 reported that both aspirin and codeine likewise failed to provide relief. (These latter 2 patients, however, as

was the case for many of this group, received only one initial dose of choline salicylate.)

The average time from the administration of the initial dose until the onset of effective relief was 29 minutes. In this group 16 patients received one initial dose (of whom 13 reported complete relief), and 12 received two or more doses. The duration of relief in these 12 cases averaged 3.3 hours after each dose.

In the second group, 22 patients received the medication for various symptoms of different etiology. Fifteen patients (68 per cent) reported complete relief of pain and malaise. In 5 of these patients with upper respiratory infections and with temperatures up to 102 F., a strong antipyretic action was observed. Within 20 minutes after the first dose, the temperature dropped an average of 2 F. The remaining 7 patients of this group reported partial relief of pain and generalized malaise.

In this group of 22 patients the average time from the administration of the first dose until the onset of effective relief was 31 minutes. The duration of relief averaged four hours after each dose.

In the entire series of 50 patients, no cases of sensitivity or allergic reaction or other side effects occurred. Four patients, including 1 with an active duodenal ulcer, 1 with a severe gastritis, and 2 with a history of allergy to aspirin, had not previously been able to tolerate even small dosages of acetylsalicylic acid. The tolerance of all 4 of these to choline salicylate was excellent. Seventeen patients expressed a definite preference for choline salicylate over previously administered aspirin. Twenty-nine patients expressed preference for neither drug and 4 stated that they preferred acetylsalicylic acid. The preferences for choline salicylate were stated to be based on the lack of side effects, the ease of administration, the rapidity of action, and the apparently greater effectiveness of the drug.

SUMMARY AND CONCLUSIONS

The effects of choline salicylate have been evaluated in a series of 50 ambulatory patients with pain and similar complaints of an acute nature. Twenty-eight of these patients complained of headache and the other 22 were patients with generalized malaise from upper respiratory infections or with complaints of pain from various miscellaneous conditions. These patients were treated, with few exceptions, with a dosage of 1 teaspoonful (870 mg.) of choline salicylate, repeated as required every four hours.

In the entire series, choline salicylate provided complete relief from pain and/or malaise in 40 patients (80 per cent) and partial relief in 7 (14 per cent). Only 3 patients (6 per cent) failed to obtain relief. In the group with headache, 89 per cent reported complete relief, and in the other group of 22, 68 per cent reported complete and 32 per cent partial relief of their complaints.

Effective analgesic activity was manifest within a very short period after administration of the first dose. The onset of such action occurred significantly earlier than would have been anticipated from previous experience with acetylsalicylic acid. In 5 febrile patients, an average drop in temperature of 2 F. was noted within 20 minutes after the first dose.

No evidences of gastric distress, allergic reactions, or other intolerance were noted. Choline salicylate was well tolerated in 4 patients, 1 with an active duodenal ulcer, known to be previously intolerant to acetylsalicylic acid. Thirty-four per cent of the patients expressed a preference for choline salicylate over aspirin and only 8 per cent expressed a preference for the latter.

This preliminary clinical study indicates that choline salicylate is a very well-tolerated, effective, very rapidly acting analgesic and antipyretic agent. It is strongly recommended for further trial and use in acute episodes in which salicylates appear to be indicated.

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Loans for Interns and Residents

A loan fund recently established by Merck & Co. is expected to benefit young physicians in training who need financial help for postgraduate study. The fund is expected to help 75 to 100 interns and residents each year who want to take postgraduate training at certain specified teaching hospitals. The universities participating in the plan are Boston, California, Chicago, Columbia, Cornell, Harvard, Illinois, Johns Hopkins, New York, Northwestern, Pennsylvania, St. Louis, Tufts, Vanderbilt, Vermont, Virginia, Washington, and Yale. Graduates of other medical schools are eligible for loans if they take an internship or residency at any of the participating universities. Funds will be processed by deans of the various medical schools who will designate the recipient and terms of the loan.

Preliminary Pharmacological Comparison of Choline Salicylate with Acetylsalicylic Acid

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Salicylates and aspirin in particular continue to be not only the most widely used of all drugs but also agents of undoubted and great value in the symptomatic and therapeutic treatment of some of the more common ailments. Recently, there has been made available a new salicylate, choline salicylate,* which has been said to possess definite advantages. Unlike aspirin, it may be administered as a stable, palatable fluid. It has been stated to be absorbed at least five times as rapidly as aspirin and yet readily to maintain therapeutic blood levels.[1–3] Thus, it would appear ideally adapted for rapid effectiveness in acute situations and for maintenance of effect in chronic conditions. Moreover, it has been stated that many patients, particularly those susceptible to gastric distress, tolerate considerably larger dosages of choline salicylate than of aspirin.[1–5] This would enable the clinician to obtain enhanced efficacy in cases where equivalent dosages of acetylsalicylic acid could not be prescribed because of the severe side effects that would ensue.

We have had an opportunity to observe some of the effects of choline salicylate and wish briefly to report some of our preliminary experiences, which, in certain respects, are completely in agreement with some of the afore-mentioned reports.

MATERIAL AND METHODS

The choline salicylate used in these studies was supplied in the form of a cherry-flavored solution, each teaspoonful (5.0 ml.) of which contained 870 mg. of active material, the equivalent in salicylate content of 10 gr. of aspirin. For the blood level studies, 5 fasting adult patients with chronic complaints of low back pain were given 2 teaspoonfuls of choline salicylate followed by water. Venous blood was collected at 12 and 60 minutes thereafter. After a rest of a few days, to permit elimination of all salicylate, the patients then were given the equivalent amount of salicylate in the form of four 5-gr. aspirin tablets, again followed by water. Venous blood samples were once more collected from each patient at 12 and 60 minutes after swallowing the complete dose. Plasma salicylate levels were determined in each sample by the method of Keller.[6]

For the clinical studies, we selected a small sample of 9 patients representing predominantly low back syndromes of long standing, clinically compatible with lumbar discs. All of these patients had received various medications in the past with no substantial improvement or satisfactory degree of relief. As a result, with no striking improvement anticipated, these patients were used primarily to demonstrate

* The trade name of The Purdue Frederick Co. for choline salicylate is Arthropan. The drug was supplied for this study by this firm.

TABLE I

Total Plasma Salicylate Levels (mg./100 ml.) After Oral Administration of 1.743 gr. of Choline Salicylate (Equivalent to 20 gr. of Acetylsalicylic Acid) and 20 gr. of Acetylsalicylic Acid

	12 minutes		60 minutes	
Subject	Choline salicylate	Aspirin	Choline salicylate	Aspirin
1	0.6	0.0	14.0	10.6
2	3.4	0.6	12.8	5.4
3	6.8	1.2	12.8	7.0
4	2.4	0.0	16.4	11.2
5	10.6	0.0	14.8	4.8
Mean	4.76	0.36	14.16	7.8
Standard error	1.78	0.24	0.669	2.02

their tolerance to choline salicylate rather than as a measure of any change in their clinical status. The patients were maintained for the first two weeks on aspirin (15 gr. four times daily) and for the second two weeks on the equivalent amount of choline salicylate (7.5 ml. four times daily). Since we were not primarily concerned with a therapeutic trial, no attempt was made to increase the dosage in an effort to obtain enhanced effectiveness even when the drug was well tolerated as given.

RESULTS

The results of the blood level studies are presented in table I. It is apparent that they essentially confirm previous reports of the much more rapid rate of absorption of choline salicylate as compared to aspirin. Thus, at the end of 12 minutes, the mean plasma salicylate level after choline salicylate was 4.76 mg./100 ml. as contrasted with only 0.36 mg./100 ml. after aspirin. After one hour, the mean level of 14.16 mg./100 ml. after choline salicylate was appreciably higher than that of 7.8 mg./100 ml. after aspirin. It is noteworthy that the magnitude of these differences is such that, as in the larger groups used in previous reports,[1, 2] the difference in salicylate blood levels at 60 minutes in this small sample of 5 patients is nevertheless statistically significant ($P < 0.05$).

In the 9 patients treated with 60 gr. of aspirin and 6 teaspoonfuls of choline salicylate daily, two weeks of each, clinical improvement was equivocal in the case of each drug. However, as noted previously, no effort was made to increase the dosage of choline salicylate although it is claimed that many patients tolerate large dosages of it.

In general, side effects were minimal. Two of the patients on choline salicylate reported transient episodes of mild nausea, not considered an harassment. One patient, while on aspirin, complained of marked nausea and emesis. Another suffered such marked and consistent epigastric distress, vertigo, and tinnitus that dis-

continuation of the aspirin was necessary. Both of these latter 2 tolerated the comparable dosage of choline salicylate, the first 1 completely and the second with only an insignificant degree of tinnitus. In all instances, the liquid choline salicylate was well received and accepted.

SUMMARY AND CONCLUSION

1. Previous reports have been confirmed that choline salicylate is much more rapidly absorbed than aspirin.

2. Choline salicylate is well accepted and well tolerated at dosages providing the equivalent of 60 gr. of aspirin per day.

3. Two patients who could not tolerate aspirin tolerated the comparable dosage of choline salicylate.

4. As a stable, palatable liquid, the greatest utility of choline salicylate might appear to be in pediatric and geriatric practice.

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International Symposium to Be Held

An international symposium will be held in Milan, Italy, on June 2–4 for the purpose of reviewing the present status of biological and clinical research on drugs affecting lipid metabolism. The agenda will include four main subjects: (1) new data on cholesterol and lipid metabolism (biosynthesis, absorption, site, catabolism, excretion, abnormal pathways); (2) experimental methods for the evaluation of drugs affecting cholesterol and lipid metabolism (new analytical methods and pharmacological tests); (3) drugs affecting cholesterol and lipid metabolism in relation to the prevention and treatment of experimental atherosclerosis; and (4) clinical methods and therapeutic significance of drugs affecting cholesterol and lipid metabolism.

The Symposium, sponsored by the Institute of Pharmacology of the University of Milan, will be under the chairmanship of Prof. E. Trabucchi.

Maintaining Normal Bowel Action: A New Answer to an Old Problem

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The laxative need, though often questioned, continues to prevail. This is particularly true in geriatrics, in emotionally disturbed patients, and in postsurgical and post-traumatic patients.

There are a variety of factors that may disturb the functional integrity of the normal bowel. These may originate on a physiological, metabolic, or drug-induced basis. Furthermore, there may be various combinations of factors.

Fundamentally, there are essentially two causes of constipation: lack of initiative and lack of force, the latter being by far the most common.

Lack of initiative may be functional or neurogenic in origin. Lack of force may result from diminished smooth muscle tone and/or contractile strength or depressed neurohumoral function. In most instances of constipation these factors are intimately related and go hand in hand. This is especially true in cases involving stress and geriatrics.

DISADVANTAGES OF COMMON LAXATIVES

The various types of older laxatives commonly in use may be classified into four groups, including irritants, bulk-producing agents, lubricants, and saline cathartics. Since most of these drugs have a limited or temporary action, the persistence of the underlying factors involved in constipation may lead to habituation. Further, most of these drugs have well-known undesirable side effects.

NEW LAXATIVES

In our studies we have tried a number of new laxatives. Experience with them has formed the basis for our judgment in respect to pantothenic acid combinations, which promote acetylcholine synthesis and thus contribute directly to the normal mechanism for bowel action.

Some of the newer laxatives that have been tried clinically in our study include malt extract, malt extract with cascara, dioctyl sodium sulfosuccinate, malt extract with dioctyl sodium sulfosuccinate, and dioctyl sodium sulfosuccinate with danthron.

Danthron is the *National Formulary* name for 1,8-dihydroxyanthraquinone. It is a synthetic product, with a molecular configuration similar to that of emodin, the active ingredient of cascara, aloe, senna, and rhubarb. Danthron, working as a humoral agent, acts as a mild peristaltic stimulant. It exerts this action directly on the intrinsic nerve plexus of the colon only, in the prescribed therapeutic dosage.

Malt extract accomplished nothing; it dissatisfied the patients and created a problem in the diabetic or suspected diabetic patients. Malt extract with cascara

was found to be slightly better than cascara alone. Dioctyl sodium sulfosuccinate was noted to soften stools, but having no propulsive action, it failed to reduce the number of required enemas. We found also that malt extract with dioctyl sodium sulfosuccinate would soften stools but did not reduce enema requirements. Dioctyl sodium sulfosuccinate with danthron did reduce impactions but did not aid in promoting normal bowel function so that the laxative could ultimately be reduced or discontinued.

Few of the standard laxative agents, whether long used or recently introduced, exert fully corrective action on underlying physiological defects that may be present. These agents act by local irritation, bulk production, fluid increase, lubrication, or, in the case of danthron, as a specific nerve plexus energizer.

PANTOTHENIC ACID IN BOWEL FUNCTION

Lack of appreciation of certain factors in bowel physiology has blocked full consideration of the constipation problem in older patients beyond the mere relief measures necessary to "move the bowels." Recent investigations of Lipmann et al[1] have focused attention on the possibility of applying new knowledge to the promotion of normal bowel action. Their findings showed that pantothenic acid is an essential precursor of coenzyme A, which is required for acetylation processes.

Acetylcholine is well recognized as being necessary for the functional activity of enteric muscles, as well as of neuromuscular mechanisms generally. Bean, Hodges, and Daum[2] have emphasized the significance of pantothenic acid in this regard by demonstrating clinically in human beings a depression of acetylation processes in experimental pantothenic acid deficiency in volunteer subjects.

The formation of acetylcholine required for the conduction of nerve impulses in the bowel muscle reflexes appears to depend on adequate pantothenic acid for coenzyme A formation, as emphasized by Zucker.[3] Although it now seems conclusive that pantothenic acid is essential for coenzyme A activity, the quantitative physiological requirements for it remain unknown. There appears, however, to be increasing evidence that both the importance and physiological requirements for pantothenic acid have been underestimated.

In older people with chronic constipation it is possible for subclinical deficiencies of pantothenic acid to occur on the basis of several factors: (1) repeated use of cathartics, causing decreased absorption of essential metabolic factors from the intestine; (2) inadequate nutrition, improper diet, and inadequate amounts of essential vitamins; (3) absence of adequate food supplementation; (4) vitamin losses in the processing of foods; and (5) interference of pantothenic acid from intestinal bacterial flora by overuse of antibiotics or other antibacterial agents. The surprising response of postoperative intestinal atony and distention to pantothenic acid after major abdominal surgery suggests that the body stores very little of this coenzyme A precursor.

DANTHRON WITH PANTOTHENIC ACID

Our experience with danthron suggested that this synthetic laxative would be

very effective, particularly if used with pantothenic acid, for the purpose of providing coenzyme A formation for adequate synthesis of acetylcholine in sufficient amount for satisfactory and normal bowel function. In light of these considerations, it seemed worth while to study the value of a danthron–pantothenic acid combination* for the relief of chronic constipation in hospitalized geriatric bed patients, for whom good histories of previous use of various cathartics were available, and in a second, larger group composed of general hospitalized patients.

The objective of this study was not only to obtain overnight relief with a laxative but also to rehabilitate the patient, if possible, by restoring a more satisfactory and normal physiological bowel activity.

CLINICAL STUDIES

The subjects for this clinical study, which extended over a period of slightly more than two years, were predominantly geriatric patients hospitalized for varying lengths of time. The clinical study involved an evaluation of laxative responses obtained from two groups of patients.

The usual dosage for all patients was 1 tablet after the evening meal. Each tablet contained 25 mg. of d-calcium pantothenate and 75 mg. of danthron.

Group 1 was composed of 48 geriatric patients who had been hospitalized for a long time and who were selected on the basis of previous histories involving the use of cathartics and also on the basis of our own clinical experience with these patients on some of the newer laxative combinations. The patients generally were afflicted with various aspects of senility including arteriosclerosis and other degenerative diseases. Twenty-two of the 48 geriatric patients were female patients who were regularly constipated and who had previously been given a variety of laxatives. Ten of these 22 female patients required complete bed rest and 6 were moderately ambulatory. The remaining 26 patients of this group were men who had received a variety of cathartics for long-standing constipation. Twenty of these 26 were bed patients.

Group 2 consisted of 355 patients in general hospital population, of whom 90 per cent were geriatric.

RESULTS

The over-all results are based on daily patient responses, with neither nurses nor attending physicians knowing what medication was being used. In fact, the tablets were similar to many that had been used in the previous control studies with some of the new laxative agents. All data were compiled and collected from patient records and charts, nursing notes, and staff notes. The data are summarized in tables I and II. In an effort to conserve space, details have been omitted but will be supplied by the author on request.

Group 1. Of this group of 48 geriatric patients, bedfast because of spinal cord diseases, strokes due to syphilis, hypertensive states, embolic phenomena, cardiac

* The trade name of The Warren-Teed Products Co., Columbus, Ohio, for a danthron–pantothenic acid combination is Modane. The drug was supplied for this study by this firm.

TABLE I

Clinical Observations on Bowel Action in Senile Chronically Constipated Patients (Group 1) After Combined Therapy with d-Calcium Pantothenate and Danthron

Subgroup	Number of constipated patients	Age, yr.	Number bedridden	Effect in reducing impactions and enemas		
				Marked	Fair	None
I (Female)	8	57–77	5	8	0	0
II (Female)	14	46–93	8	13	0	1
III (Male)	26	45–90	20	14	5	7
Total	48		33	35	5	8

arrhythmia, or trauma, 35 obtained marked relief, 5 fair relief, and in 8 there was no response in reducing bowel impaction and necessity for enemas (see table I). In the patients who responded, the stools were soft, easily expelled, and were not watery or associated with additional gas or tenesmus.

One patient did not respond to any type of laxative and continually had impaction. Two patients developed a slight rash about a week after therapy was started. This was corrected, however, with change in diet. Continuance of the pantothenate-danthron combination under these circumstances did not cause a reappearance of the rash. No other side effects that could be referred to the pantothenate-danthron therapy were noted at any time.

Group 2. In this group of 355 general hospital patients, of whom 90 per cent were geriatric, the administration of pantothenic acid with danthron gave marked relief in 330 patients, fair relief in 14, and no relief in 11 (see table II). Thus 93 per cent of the patients obtained effective response characterized by absence of significant side effects, reduction of enema requirements in 80 per cent, and complete absence of impactions.

CONCLUSION

As was previously stated, the fundamental causes of constipation are lack of initiative and lack of force. The majority of deconstipating agents merely relieve the clinical manifestations of constipation while doing nothing to rehabilitate the precipitating physiological mechanism.

In view of the pharmacological and physiological aspects suggested by the com-

TABLE II

Clinical Observations on Bowel Action in General Hospital Patients (Group 2) After Combined Therapy with d-Calcium Pantothenate and Danthron

Number of constipated patients	Age, yr.	Effect in reducing impactions and enemas		
		Marked	Fair	None
355	30–85	330	14	11

bination of danthron and pantothenate, the objective sought—relief plus rehabilitation—was more satisfactorily attained.

As was expected, this combination proved extremely useful in handling the chronic constipation in older persons. It seems to promote normal bowel activity without any significant side actions. The drug is easily administered.

In our experience, this combination has been more satisfactory in handling chronic constipation of senile bedridden patients than most other laxatives, either singly or in combination.

SUMMARY

1. A comparative study of several new laxatives proposed for chronically constipated hospitalized patients was carried out over a period exceeding two years.

2. A combination of d-calcium pantothenate, 25 mg., and danthron, 75 mg., was found to be the most satisfactory laxative.

3. A 93 per cent effective laxative response was obtained in a general hospital population, and an 80 per cent effective laxative response was obtained in bedfast geriatric patients with various degenerative diseases.

4. The pantothenate-danthron combination is characterized by absence of significant side effects, reduction of enema requirements, and a low incidence of impactions.

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SYMPOSIUM ON MEDICINE AND WRITING

The Symposium on Medicine and Writing that appeared in the November 1956 issue of International Record of Medicine has been published recently as a Monograph. The articles included in this Monograph are: "The Editing of a Modern Medical Textbook" by Russell L. Cecil; "Plain Talk and Clear Writing" by Morris Fishbein; "The Principles of Bibliographic Citation" by John F. Fulton; "The Art of Communication" by Joseph Garland; "On Writing a History of Medicine" by Douglas Guthrie; and "Minerva and Aesculapius: The Physician as Writer" by Félix Martí-Ibáñez.

This 72-page Monograph is sold for $3.00. As the fourth in the series of MD International Symposia, this book is the companion piece of *Medical Writing*, which was published in May 1956.

To obtain this monograph, write to MD Publications, Inc., 30 East 60th Street, New York 22, N. Y.

FOOD SUPPLEMENT. Growth disturbances in adolescent and pre-adolescent children ingesting inadequate unbalanced diets may be corrected by supplementing the daily food intake with nonfat dry milk, according to a recent report (J. Dis. Child. 98:187, 1959). Skeletal and somatic growth were both accelerated in 10 children aged 4 to 12½ years who were given 6 oz. of milk six days a week for six months. An increased rate of body growth was noted in children aged 15 to 16 years, but rate of skeletal maturation was unchanged.

MUSCLE RELAXANT. Indicated for relief of pain and spasm in a wide range of musculoskeletal disorders is carisoprodol (Rela, Schering). The drug is reported to be approximately eight times more active than either meprobamate or mephenesin in relaxing induced spasticity in animals. The compound's analgesic action differs from that of morphine and its derivatives and salicylates: it appears to modify central pain perception without effecting peripheral pain or withdrawal reflexes. Side effects noted in clinical tests to date have been minimal.

IMPROVING CORONARY BLOOD FLOW. The "planting" of strips of stomach lining in the heart muscle to improve its blood supply was reported by Frances E. Knock (Chicago) at the recent meeting of the American College of Surgeons. The operation is being studied as an aid to hearts with inadequate coronary blood flow, since it appears to bring more blood to the hearts of animals than several other procedures tested.

RADIATION TRAUMA. A thyroid hormone (triiodothyronine) aids healing in skin conditions caused by excessive exposure to x-rays, according to the recent biennial report of the Sloan-Kettering Institute for Cancer Research. More than half of 75 patients with late radiation damage of 2 to 30 years' duration showed good to excellent amelioration of lesions when treated with the hormone.

BURN TREATMENT. The synthetic and relatively nonandrogenic steroid norethandrolone (Nilevar, Searle) was administered to 31 of 33 of the school children burned in the fire at Our Lady of the Angels School in Chicago (J. Internat. Coll. Surgeons 32:359, 1959). The drug produced an average weight gain of 14.6 per cent compared with no weight gain in the 2 patients not receiving the drug. Dosage was 10 to 20 mg./day and the drug was usually given for 8 to 12 weeks.

Healing of wounds seemed to occur more rapidly in patients receiving norethandrolone.

HEART MICROPHONE. A microphone no larger than a grain of rice, which is introduced into the heart at the tip of a catheter to permit listening to the heart sounds from the inside, has facilitated diagnosis of certain inborn heart defects in nearly 5000 children, including a 1-day-old infant, according to a recent report by David H. Lewis (Philadelphia), an American Heart Association Established Investigator. With this technique, defects can be distinguished and a correct diagnosis can be made at a far earlier age than is possible otherwise.

NEW METHOD OF ADMINISTERING VITAMIN A. Injecting laboratory rats with vitamin A along with a compound to keep it in suspension gave as good results as the common orally administered dose, according to a recent report (Nature 185:249, 1960). When vitamin A is given orally, it is difficult to judge how much is lost through faulty absorption or through failure to break down the oil in which the vitamin is dissolved. The report suggests that the new injection method could be useful in persons who require therapeutic dosages of the vitamin.

NEW PREGNANCY TEST. In a new test for the detection of pregnancy, a freshly voided random sample of urine is brought to room temperature, adjusted to a pH of 4.0, and charged for five seconds with 12 volts direct current electricity applied through silver and copper electrodes (Am. J. Obst. & Gynec. 78:1250, 1959). The urine of pregnant women causes a black substance to be deposited on the anode. The test yielded an 84.0 per cent accuracy among 125 women in the first three months of pregnancy, including those with complications.

SPASMOLYTIC. Now available is valethamate bromide (Murel Sustained Action Tablets, Ayerst), indicated for spasm of the gastrointestinal, genitourinary, and biliary tracts and in active, latent, or incipient peptic ulcer. The sustained-action tablet provides prompt, continuous, and prolonged action for six to nine hours.

ORAL ANDROGEN FOR BREAST CANCER. Fluoxymesterone (Halotestin, Upjohn), a new oral androgen, has been found effective in suppressing advanced mammary cancer in postmenopausal patients (Surg., Gynec. & Obst. 109:235, 1959). Remission occurred in 7 of 23 patients, in 2 of them after hypophysectomy. Fluoxymesterone appears to be less masculinizing than injectable androgens in therapeutic doses. Fluoxymesterone can cause liver dysfunction such as is seen with methyltestosterone.

Clinical Effectiveness of a Tetracycline-Oleandomycin Combination in Pediatrics with Particular Consideration of Severe Infections

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In view of the increasing number of failures of antibiotics in the treatment of severe bacterial infections, it appeared worth while to study a combination of tetracycline and oleandomycin (Signemycin*) in order to obtain data on its clinical efficacy in pediatric patients. In March, 1957, when we started using this new drug, there were no reports on experience with this preparation in the field of pediatrics. Since then, several have appeared.

In this paper we shall report on 216 patients treated with a liquid oral preparation of tetracycline-oleandomycin and appraise the drug's efficacy in a controlled study on 50 patients with primary staphylococcal pneumonia.

Tetracycline-oleandomycin has been available in the form of capsules, sirup, drops, and a preparation for intravenous use. We have used it in 854 patients, intravenously in 74 of these. The oral dosage was 25 to 50 mg./Kg./day in the less severe cases, 50 to 100 mg./Kg./day in the more severe cases; the intravenous dosage varied from 20 to 50 mg./Kg./day.

The patients who were treated with tetracycline-oleandomycin were selected on the basis of the following criteria: patients with bacterial infections that previously had been responding poorly to single antibiotics, e.g., patients with primary staphylococcal pneumonia, osteomyelitis, and sepsis; patients not responding to usually effective agents, e.g., patients with pneumonia or otitis media treated with penicillin; patients with conditions requiring immediate intensive antibiotic treatment, e.g., infants less than 1 year old with bronchopneumonia or pneumonia occurring during measles or whooping cough; premature infants or newborn infants with birth trauma, the antibiotic combination being given as prophylaxis against infection.

Final selection of patients to be included in the analysis was made as follows: After having administered tetracycline-oleandomycin for one year, we felt that its clinical efficacy was very satisfactory. At this time, the oleandomycin component of liquid tetracycline-oleandomycin preparation for oral use became available in the triacetate form, ingestion of which reportedly resulted in even higher serum levels than did the previous preparation. From then on (April, 1958), all patients to be treated orally received the triacetate preparation. On the basis of the criteria just given, 216 patients received it up to February, 1959. These children were the group analyzed first. Not included in this group were the newborn infants with birth trauma and the premature infants who received tetracycline-oleandomycin as pro-

* The trade name of Chas. Pfizer & Co., Inc., for the combination of tetracycline and oleandomycin is Signemycin.

TABLE I

Response of 216 Pediatric Patients to Oral Tetracycline-Oleandomycin

Condition	Total cases	Result*		
		Very good	Good	Not satisfactory
Bronchopneumonia	70	38	31	1
Lobar pneumonia	3	3	—	—
Suppurative staphylococcal pneumonia	17	5	6	6
Aspiration pneumonia (in newborn infants)	14	4	7	3
Pertussal pneumonia	10	4	4	2
Pneumonia during measles	4	3	—	1
Suppurative infection of skin and omphalitis	35	34	1	—
Urinary infection	14	7	5	2
Lymphadenitis and pharyngeal infection	15	13	2	—
Infection of the middle ear	31	17	10	4
Osteomyelitis	2	—	2	—
Typhoid fever	1	1	—	—
	—	—	—	—
	216	129	68	19

* Very good = completely cured, significantly improved within the first three days of therapy; good = completely cured, significantly improved between the fourth day of treatment and the end of the second week of therapy; not satisfactory = no response, insufficient effect of treatment, development of resistance, relapses.

phylaxis against infection, the patients who received intravenous tetracycline-oleandomycin, and the children who took other antibiotics in addition.

The second group to be analyzed consisted of 50 patients with primary staphylococcal pneumonia. They were all less than 1 year old, and they all entered our hospital within two or three days after onset of disease and were treated immediately. Excluded from the analysis were infants who had received other antibiotics prior to tetracycline-oleandomycin. Twenty-four patients were given tetracycline-oleandomycin (including 7 treated intravenously or with capsules), while 26 others were given other antibiotics.

Table I indicates the response to oral tetracycline-oleandomycin of patients of the pediatric age group. Of 70 patients with bronchopneumonia, 47 were less than 1 year old and 29 were less than 3 months old. In all 6 cases of umbilical infection and all 12 of pyodermia, hemolytic *Staphylococcus aureus* was cultured. In all 14 cases of urinary tract infection, the urinary findings had remained unchanged in spite of at least two weeks' treatment with sulfonamides.

Whereas in most cases the drug could be discontinued after 6 to 10 days of treatment, more severe infections such as primary staphylococcal pneumonia had to be treated for several weeks.

Table II compares the results after treatment of primary staphylococcal pneumonia in 24 patients who received tetracycline-oleandomycin and 26 patients who received other antibiotics. The numbers in each group are small and thus the differences are not amenable to statistical evaluation. There was, however, an apparent and consistent tendency for the patients treated with any of the other three antibiotics not to respond as well as those who received tetracycline-oleandomycin. This permits the assumption that tetracycline-oleandomycin was superior in the treatment of primary staphylococcal pneumonia. After five to six weeks of treatment with tetracycline-oleandomycin, resistant staphylococci were recovered, from all 6 cases of therapeutic failure in the tetracycline-oleandomycin group, by needle aspiration of encapsulated pus in lung tissue and/or the pleural space. As far as side reactions are concerned, we observed vomiting twice and an allergic exanthema once in children given the oral preparation, and temporary redness and edema along the veins used for infusion was noted in a few of the 74 patients treated intravenously, but only when large amounts had been given for longer than a week.

DISCUSSION

Treatment of 216 patients with the antibiotic combination tetracycline-oleandomycin was very effective. Since control groups treated with other antibiotics are lacking, we cannot compare the differences in therapeutic efficacy between our group of children treated with tetracycline-oleandomycin and patients treated with other antibiotics. However, anyone who is familiar with the difficulties encountered in antibiotic treatment of the conditions mentioned here will readily appreciate our gratification with the high rate of cure reported here.

Table II indicates the superiority of tetracycline-oleandomycin over other antibiotics, even though the patient groups were small. We selected primary staphylococcal pneumonia for this controlled study because this condition has continually raised the problem of poor response to antibiotics.

This favorable response to tetracycline-oleandomycin may have been due to greater diffusion of the antibiotic combination or to presence of strains of bacteria not yet

TABLE II

Comparison of Results of Treatment of 24 Patients with Primary Staphylococcal Pneumonia with Tetracycline-Oleandomycin and of 26 Patients with Other Antibiotics

Antibiotic used	Number of patients	Result		
		Very good	Good	Not satisfactory
Tetracycline-oleandomycin combination	24	9	9	6
Other antibiotics				
Tetracycline	14	1	6	7
Erythromycin	8	2	2	4
Penicillin-streptomycin combination	4		1	3
	26	3	9	14

resistant to tetracycline-oleandomycin or even to retarded development of bacterial resistance to this combined antibiotic. The explanation may be found after studies of larger groups and longer experience with combinations of antibiotics in diseases not responding to single antibiotics.

SUMMARY

In March, 1957, at the municipal children's hospital in Schwabing (Munich), a combination of tetracycline and oleandomycin was introduced in therapy. As of September, 1959, it had been administered to 854 patients up to the age of 14. The drug was available in the form of capsules, sirup, drops, and a preparation for intravenous use.

Results in 216 patients treated orally with a newer form of the preparation, containing the triacetate of oleandomycin, are reported. A controlled study of 50 patients with primary staphylococcal pneumonia is analyzed. The favorable results are discussed.

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BOOK REVIEWS

Textbook of Pathology with Clinical Applications. STANLEY L. ROBBINS, M.D. Philadelphia, W. B. Saunders Company, 1959.

This book departs from the usual textbook of pathology in both organization of subject matter and the treatment of individual chapters. The author has made a special effort to achieve a logical sequence of chapters in which no discussion presupposes a knowledge of the material that is to appear at a later point in the book. Systemic diseases are presented in their entirety and not discussed piecemeal under each organ, to enable the complete picture to be presented at one time.

The initial chapters present basic pathological principles, and later chapters, the individual organs or systems applying to these principles. Each chapter presents the nature of the lesions, the picture of the norm, the determining pathology, and, finally, the correlation with clinical problems. The clinical-pathological correlation reveals what diseases do to bodily tissues with a view toward correlating these changes in the living patient. The remarkable feature of the book is the dynamic presentation of tissue changes in disease, which makes morbid pathology as vivid as clinical medicine.

Each system of the body is adequately interpreted, structurally and functionally, in succinct form to enable ready perusal for clinical orientation. It is truly a didactic book, well written, clearly illustrated, and beautifully integrated—a credit to both author and publisher—*I. Newton Kugelmass, M.D.*

Review of Physiological Chemistry. HAROLD A. HARPER, PH.D. Ed. 7. Los Altos, Calif. Lange Medical Publications, 1959.

Advances in biochemistry are continuing at such an accelerated pace that books frequently become out-of-date before they are published. This is not so with Harper's new edition because it presents a critical and concise summary of the essential advances in our expanding universe of physiological chemistry. It will enhance, supplement, or complement standard texts in biochemistry. The material is offered in lucid form, drawn from the author's postgraduate lectures to physicians.

The book is important because it presents the dynamic aspects of biochemistry applicable to everyday practice. It is one of the few that embodies biochemistry in clinical discipline because the author understands and integrates both fields. Each aspect of biochemistry is included as well as tissue function tests, metabolism, nutrition, and hormone and tissue chemistry.

The book is well written, beautifully illustrated, clearly documented, and a credit to both author and publisher.—*I. Newton Kugelmass, M.D.*

Metabolic Care of the Surgical Patient. FRANCIS D. MOORE, M.D. ILLUSTRATED BY MILDRED CODDING, A.B., M.A. Philadelphia, W. B. Saunders Company, 1959.

This unique volume is a masterly contribution on the mechanism and management

of surgical problems in everyday practice. It is a guidebook to the thoughtful surgeon for the metabolic care of his patients. The entire focus is on the integrated patient in distress rather than on the surgical pathology or the procedures available to correct it. The range of the disorders covers most of the metabolic situations encountered on a general surgical service including problems in neurology, orthopedics, and neurosurgery. The author presents such topics as fluid volume, blood volume, nutrition, and tissue injury in their respective places throughout the discussions of management. The clinical basis for this contribution rests entirely on the author's group of studies embodied in a previous monograph on the *Metabolic Response to Surgery*. The present book is an extension of these concepts presenting answers to questions raised by surgeons everywhere.

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This monumental work integrates the surgical contributions of a modern school of scientific thought applied to surgical procedures in the cause of complete reversibility of tissues after injury. The style is clear and lucid, the illustrations striking and revealing, the presentation stimulating and beneficial.—*I. Newton Kugelmass, M.D.*

Bacterial and Mycotic Infections of Man. EDITED BY RENÉ J. DUBOS, PH.D. Ed. 3. Philadelphia, J. B. Lippincott Company, 1958.

This remarkable volume is most revealing of our newer knowledge of the bacteria, actinomycetes, and molds pathogenic for man and diverse infectious phenomena characteristic of this group of organisms. An expert in each field crystallizes our current concepts of medical microbiology. The masterly dissertations unravel host-parasite relationships rather than the characteristics of the microorganisms per se. But the properties of the parasites are well correlated with their pathogenic behavior and with the multiple manifestations of the response of the invaded host to their constituents. Each chapter presents clearly the problems concerning the parasite and host in accompanying infectious diseases.

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presence. Tuberculosis illustrates the acute exudative and chronic proliferative pathological processes accompanying infection, as well as the altered reactivity, allergy, of the body that results from previous exposure to the bacillus.

The authors maintain that the ability of microorganisms to produce pathological changes is under the influence of large biological forces, which do not always manifest themselves in the form of recognized immunochemical reactions. The book is clearly written, beautifully illustrated, and well documented. Each of the 37 contributors from the various medical centers of this country have done a great academic service to both student and clinician in making the essence of bacterial and mycotic infections so accessible—*I. Newton Kugelmass, M.D.*

Collected Papers of the Mayo Clinic and the Mayo Foundation. Volume 50, 1958. Philadelphia and London, W. B. Saunders Company, 1959. Pp. 791. Price $13.00.

This valuable book contains the collected papers of members of the Mayo Clinic and the Mayo Foundation for the year 1958. The outstanding quality of this collection is an excellent index of the important work being carried out at these institutions in every area of medical science.

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The book includes 24 complete articles, 76 in abridged form, 9 abstracts, and a list of 570 by title. Format and typography are excellent, and a thorough index is included.

The Diabetic's Handbook. ANTHONY M. SINDONI, JR., M.D. Ed. 2. New York, The Ronald Press Company, 1959. Pp. 285. Price $4.50.

The Diabetic's Handbook is an excellent guide for diabetic persons in helping them to understand their illness and to learn to manage it.

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